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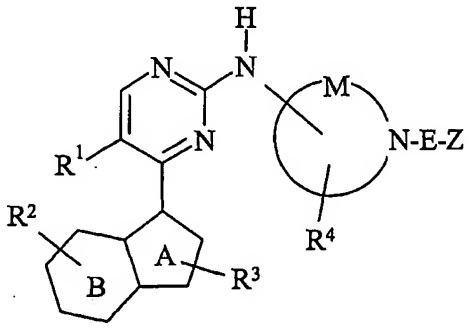
(54) Title: AMINOPYRIMIDINE DERIVATIVES AS JNK INHIBITORS



(I)

(57) Abstract: A compound of formula (I) or a pharmaceutically acceptable salt, solvate or N-oxide thereof: wherein A represents a pyrrole, pyrazole, imidazole or triazole ring; B represents a benzene, pyridine or pyrimidine ring; M represents the residue of an azetidine, pyrrolidine or piperidine ring; E represents a covalent bond or an optionally substituted straight or branched alkylene chain containing from 1 to 4 carbon atoms; Z represents hydrogen, -CORa, -$C0_2R^b$, -$CONK^cR^d$, -$CONR^cOR^b$, -$COCO_2R^b$, - $COCONR^cR^d$, -$COCH2NR^cR^d$, -$COCH2NR^cCONK^cR^d$, $COCH2NR^cCO_2R^b$, -NR^cCOR^a, - NR^cCO2R^b, -$NR^cCONR^cR^d$, -$S0_2R^e$, -$SO_2NR^cR^d$ or -$SO2NR^cC0_2R^b$; or Z represents an optionally substituted phenyl, heteroaryl or C_{3-7} heterocycloalkyl group; R^1 and R^2 independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, aminocarbonyl or C_{2-6} alkoxycarbonyl; R^3 represents hydrogen, C_{1-6} alkyl, -$CH2CONR^cR^d$ or -SO_2R^e; R^4 represents hydrogen, C_{1-6} alkoxy, oxo, -$CO2R^b$ or -$CONK^cR^d$. The compounds of the present invention are potent inhibitors of JNK.

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AMINOPYRIMIDINE DERIVATIVES AS JNK INHIBITORS

The present invention relates to a class of substituted aminopyrimidine derivatives and to their use in therapy. More particularly, the invention provides 2-aminopyrimidine derivatives which are substituted in the 4-position by a fused bicyclic heteroaromatic moiety. These compounds are selective inhibitors of c-Jun NH_2-terminal kinase (JNK) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, vascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions.

The JNK pathway is implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases (cf. A.M. Manning & R.J. Davis, *Nature Reviews: Drug Discovery*, 2003, **2**, 554-565).

The compounds in accordance with the present invention, being potent and selective JNK inhibitors, are therefore of use in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; vascular disorders; neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma and seizures; metabolic disorders such as obesity and type 2 diabetes; oncological conditions including leukaemia, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, colon, prostate and ovary; pain and nociceptive disorders; and ophthalmic disorders including age-related macular degeneration (ARMD).

In addition, the compounds according to the present invention may be used as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds according to this invention may be useful as radioligands in assays for detecting compounds capable of binding to human JNK enzymes.

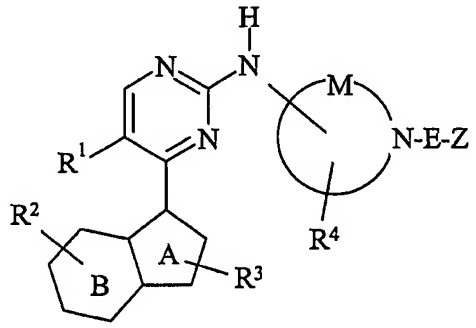
The prior art is replete with 2-aminopyrimidine derivatives, which have been described as being of use *inter alia* as kinase inhibitors. Recent examples include WO 2004/041814; WO 2004/041810; WO 2004/041789; WO 2004/016597; WO 2004/005283; US-A-2003/0199511; WO 03/082855; WO 02/102313; WO 02/092573; WO 02/083668; WO 02/083667; WO 02/079197; WO 02/46184; WO 02/30358; WO 01/60816; WO 01/47921; and WO 01/12621; as well as WO 92/01675. There has, however, been no specific disclosure to date of a 2-(heterocyclylamino)pyrimidine derivative substituted in

the 4-position by a fused bicyclic heteroaromatic moiety wherein the heteroaromatic moiety is attached to the pyrimidine nucleus via a five-membered ring [cf. the ring designated "A" in the compounds of formula (I) below]. It has now been found that such compounds are particularly valuable as selective inhibitors of JNK enzymes.

The compounds according to the present invention are potent and selective JNK inhibitors having a binding affinity (IC_{50}) for the human JNK1 and/or JNK2 and/or JNK3 enzyme of 5 μM or less, typically of 1 μM or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20nM or less (the skilled person will appreciate that a *lower* IC_{50} figure denotes a *more active* compound). The compounds of the invention may possess at least a 10-fold selective affinity, typically at least a 20-fold selective affinity, suitably at least a 50-fold selective affinity, and ideally at least a 100-fold selective affinity, for the human JNK1 and/or JNK2 and/or JNK3 polypeptide relative to other human kinases.

International patent application WO 2004/089913, published 21st October 2004, discloses a class of 2-aminopyrimidine derivatives as IKK inhibitors.

The present invention provides a compound of formula (I), or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof:



(I)

wherein

A represents a pyrrole, pyrazole, imidazole or triazole ring;

B represents a benzene, pyridine or pyrimidine ring;

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

E represents a covalent bond or an optionally substituted straight or branched alkylene chain containing from 1 to 4 carbon atoms; wherein the optional substituents are

selected from cyano, aminocarbonyl, C_{1-6}alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl;

Z represents hydrogen, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-COCO_2R^b$, $-COCONR^cR^d$, $-COCH_2NR^cR^d$, $-COCH_2NR^cCONR^cR^d$, $-COCH_2NR^cCO_2R^b$, $-NR^cCOR^a$, $-NR^cCO_2R^b$, $-NR^cCONR^cR^d$, $-SO_2R^e$, $-SO_2NR^cR^d$ or $-SO_2NR^cCO_2R^b$; or Z represents an optionally substituted phenyl, heteroaryl or C_{3-7} heterocycloalkyl group;

R^1 and R^2 independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, aminocarbonyl or C_{2-6} alkoxycarbonyl;

R^3 represents hydrogen, C_{1-6} alkyl, $-CH_2CONR^cR^d$ or $-SO_2R^e$;

R^4 represents hydrogen, C_{1-6} alkoxy, oxo, $-CO_2R^b$ or $-CONR^cR^d$;

R^a represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

R^b represents hydrogen or C_{1-6} alkyl;

R^c is as defined above for R^a, and R^d represents hydrogen, C_{1-6} alkyl or hydroxy(C_{1-6})alkyl; or R^c and R^d, when taken together with the nitrogen atom to which they are both attached, represent azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl, any of which groups may be optionally substituted by C_{1-6} alkyl or hydroxy; and

R^e is as defined above for R^a.

One group of compounds of the invention has the formula (I), wherein:

B represents a benzene or pyridine ring;

E represents a covalent bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Z represents hydrogen, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-NR^cCOR^a$, $-NR^cCO_2R^b$, $-NR^cCONR^cR^d$, $-SO_2R^e$, $-SO_2NR^cR^d$ or $-SO_2NR^cCO_2R^b$; or Z represents an optionally substituted heteroaryl group;

R^d represents hydrogen or C_{1-6} alkyl; and

A, M, R^1, R^2, R^3, R^4, R^a, R^b, R^c and R^e are as defined above.

Another group of compounds of the invention has the formula (I) wherein R^3 represents hydrogen, $-CH_2CONR^cR^d$ or $-SO_2R^e$; R^c and R^d, when taken together with the nitrogen atom to which they are both attached, represent azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl, any of which groups may be optionally substituted by C_{1-6} alkyl; and A, B, E, Z, M, R^1, R^2, R^4, R^a, R^b and R^e are as defined above.

Where Z in the compounds of formula (I) above represents a phenyl, heteroaryl or C_{3-7} heterocycloalkyl group, this group may be unsubstituted, or substituted by one or more substituents. Typically, the phenyl, heteroaryl or C_{3-7} heterocycloalkyl group Z will be unsubstituted, or substituted by one or two substituents. Suitably, the phenyl, heteroaryl or C_{3-7} heterocycloalkyl group Z will be unsubstituted or monosubstituted. Typical substituents on the phenyl, heteroaryl or C_{3-7} heterocycloalkyl group Z include halogen, cyano, nitro, oxo, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl and C_{2-6} alkoxycarbonyl. In one group of compounds the heteroaryl group Z may be substituted by one or more, typically one or two substituents selected from halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl and C_{2-6} alkoxycarbonyl. Suitable substituents on the heteroaryl group Z include halogen, C_{1-6} alkyl, cyano, amino and nitro. Particular substituents on the heteroaryl group Z include halogen and C_{1-6} alkyl. Particular substituents on the C_{3-7} heterocycloalkyl group Z include oxo and C_{2-6} alkoxycarbonyl. Typically the phenyl group Z is unsubstituted.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy,

suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds according to the invention include straight-chained and branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylamino" and "C_{1-6} alkylsulphonyl" are to be construed accordingly.

Specific C_{3-7} cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, tetrahydrofuranyl, pyrrolidinyl, imidazolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl. Further suitable examples include tetrahydrothienyl, oxazolidinyl and dihydropyridazinyl.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl and pyrazinyl groups. Further suitable heteroaryl groups include naphthyridinyl, cinnolinyl and benzotriazolyl.

The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, especially fluoro or chloro.

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($CH_2C=O$)-enol (CH=CHOH) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

In one embodiment, ring A represents a pyrrole ring. In an additional embodiment, ring A represents a pyrazole ring. In another embodiment, ring A represents an imidazole ring. In a further embodiment, ring A represents a triazole ring, especially a 1,2,4-triazole ring.

Suitably, A represents a pyrrole, imidazole or triazole ring.

In one embodiment, ring B represents a benzene ring. In another embodiment, ring B represents a pyridine ring. In a further embodiment B represents a pyrimidine ring.

In one group of compounds of the invention B represents a benzene or pyridine ring.

Examples of fused bicyclic ring systems represented by the moiety A/B include 1*H*-indol-1-yl, 1*H*-indol-3-yl, 1*H*-indazol-1-yl, 1*H*-indazol-3-yl, pyrazolo[1,5-*a*]pyridin-3-yl, 1*H*-benzimidazol-1-yl, imidazo[1,2-*a*]pyridin-3-yl, pyrrolo[3,2-*b*]pyridin-3-yl, pyrrolo[3,2-*c*]pyridin-3-yl, pyrrolo[2,3-*c*]pyridin-3-yl, pyrrolo[2,3-*b*]pyridin-3-yl, imidazo[4,5-*b*]pyridin-1-yl, imidazo[4,5-*b*]pyridin-3-yl, imidazo[4,5-*c*]pyridin-1-yl, imidazo[4,5-*c*]pyridin-3-yl and [1,2,4]triazolo[4,3-*a*]pyridin-3-yl. A further example of a fused bicyclic ring system represented by the moiety A/B includes imidazo[1,2-a]pyrimidin-3-yl. Further examples of fused bicyclic ring systems represented by the moiety A/B include 1*H*-pyrrolo[3,2-b]pyridin-1-yl, 1*H*-pyrrolo[2,3-b]pyridin-1-yl and pyrazolo[1,5-a]pyridin-3-yl.

Particular A/B ring systems include 1*H*-indol-3-yl, 1*H*-indol-1-yl, 1*H*-benzimidazol-1-yl, imidazo[1,2-*a*]pyridin-3-yl, pyrrolo[2,3-*b*]pyridin-3-yl, pyrrolo[3,2-*c*]pyridin-3-yl, [1,2,4]triazolo[4,3-*a*]pyridin-3-yl and imidazo[1,2-a]pyrimidin-3-yl. In one group of compounds of the invention the A/B ring systems include 1*H*-indol-3-yl, 1*H*-

benzimidazol-1-yl, imidazo[1,2-*a*]pyridin-3-yl, pyrrolo[2,3-*b*]pyridin-3-yl and [1,2,4]triazolo[4,3-*a*]pyridin-3-yl. Further particular A/B ring systems include 1*H*-pyrrolo[3,2-b]pyridin-1-yl, 1*H*-pyrrolo[2,3-b]pyridin-1-yl and pyrazolo[1,5-a]pyridin-3-yl.

In one embodiment, the A/B ring system represents 1*H*-indol-3-yl. In another embodiment, the A/B ring system represents 1*H*-indol-1-yl. In yet another embodiment, the A/B ring system represents 1*H*-benzimidazol-1-yl. In an additional embodiment, the A/B ring system represents imidazo[1,2-*a*]pridin-3-yl. In a further embodiment, the A/B ring system represents pyrrolo[2,3-*b*]pyridin-3-yl. In a yet further embodiment, the A/B ring system represents pyrrolo[3,2-*c*]pyridin-3-yl. In a still further embodiment, the A/B ring system represents [1,2,4]triazolo[4,3-*a*]pyridin-3-yl. In another embodiment, the A/B ring system represents imidazo[1,2-a]pyrimidin-3-yl. In a further embodiment, the A/B ring system represents 1*H*-pyrrolo[3,2-b]pyridin-1-yl. In another embodiment, the A/B ring system represents 1*H*-pyrrolo[2,3-b]pyridin-1-yl. In another embodiment, the A/B ring system represents pyrazolo[1,5-a]pyridin-3-yl.

In one embodiment, M represents the residue of an azetidine ring, especially an azetidin-3-yl ring. In another embodiment, M represents the residue of a pyrrolidine ring, especially a pyrrolidin-3-yl ring. In a further embodiment, M represents the residue of a piperidine ring, suitably a piperidin-3-yl or piperidin-4-yl ring, especially a piperidin-4-yl ring.

Where E represents a straight or branched alkylene chain, this may be, for example, methylene, ethylmethylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or butylene. E may also represent methylmethylene. Representative examples of substituents that may be present on E include cyano, aminocarbonyl and methylaminocarbonyl.

Moreover, E may represent a covalent bond. Where E represents a covalent bond, the moiety Z is attached directly to the heterocyclic ring of which M is the residue.

In one embodiment E represents a covalent bond or an unsubstituted straight or branched alkylene chain containing from 1 to 4 carbon atoms.

Suitably, E represents a covalent bond, or a methylene, ethylmethylene or ethylene linkage. Typically, E represents a covalent bond, or a methylene linkage. In one embodiment, E represents a covalent bond. In another embodiment, E represents a methylene linkage. In an additional embodiment, E represents an ethylmethylene linkage.

In a further embodiment, E represents an ethylene linkage. In a further embodiment E represents a methylmethylene linkage.

Ideally, when E represents a covalent bond, then Z does not represent $-NR^cCOR^a$, $-NR^cCO_2R^b$ or $-NR^cCONR^cR^d$.

Selected values of R^1 include hydrogen, fluoro, chloro, cyano, nitro, methyl, ethyl, trifluoromethyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, methylsulphonyl, amino, methylamino, dimethylamino, aminocarbonyl, methoxycarbonyl and ethoxycarbonyl.

Suitably, R^1 represents hydrogen, halogen, cyano or C_{1-6} alkyl. R^1 also suitably represents C_{1-6} alkoxy. Particular values of R^1 include hydrogen, fluoro, chloro, cyano, methoxy and methyl. In one group of compounds particular values of R^1 include hydrogen, fluoro, chloro, cyano and methyl.

In one embodiment, R^1 represents hydrogen. In another embodiment, R^1 represents halogen, in particular fluoro or chloro, especially chloro. In an additional embodiment, R^1 represents cyano. In a further embodiment, R^1 represents C_{1-6} alkyl, in particular methyl or ethyl, especially methyl. In another embodiment, R^1 represents C_{1-6} alkoxy, in particular methoxy.

Selected values of R^2 include hydrogen, fluoro, chloro, cyano, nitro, methyl, ethyl, trifluoromethyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, methylsulphonyl, amino, methylamino, dimethylamino, aminocarbonyl, methoxycarbonyl and ethoxycarbonyl.

Suitably, R^2 represents hydrogen, cyano or halogen. R^2 also suitably represents C_{1-6} alkoxy, amino, C_{1-6}dialkylamino or aminocarbonyl. Particular values of R^2 include hydrogen, cyano, fluoro and chloro. Further particular values of R^2 include bromo, amino, methoxy, dimethylamino and aminocarbonyl. In one group of compounds of the invention R^2 represents hydrogen or halogen, typically hydrogen, fluoro and chloro.

In one embodiment, R^2 represents hydrogen. In another embodiment, R^2 represents halogen, in particular fluoro or chloro or R^2 represents bromo. In a further embodiment, R^2 represents cyano. In another embodiment, R^2 represents amino. In a yet further embodiment, R^2 represents C_{1-6} alkoxy, in particular methoxy. In an additional embodiment, R^2 represents C_{1-6}dialkylamino, in particular dimethylamino. In a further embodiment, R^2 represents aminocarbonyl.

In one group of compounds, R^a represents hydrogen; or C_{1-6} alkyl, aryl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Examples of typical substituents on R^a include C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, hydroxy(C_{1-6})alkyl, halogen, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, di(C_{1-6})alkylhydrazinylcarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, aminocarbonylamino, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di(C_{1-6})alkylaminocarbonyl, aminosulfonyl, C_{1-6} alkylsulfonyl and C_{1-6} alkylaminocarbonyl(C_{1-6})alkyl.

In one group of compounds, suitable substituents that may be present on R^a include C_{1-6} alkyl, C_{1-6} alkoxy, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl, di(C_{1-6})alkylhydrazinylcarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino and aminocarbonylamino.

Examples of particular substituents on R^a include methyl, methoxy, oxo, acetyl, carboxy, ethoxycarbonyl, dimethylhydrazinylcarbonyl, dimethylamino, acetylamino and aminocarbonylamino. Further examples of particular substituents include hydroxy, hydroxymethyl, 2-hydroxyethyl, fluoro, methoxycarbonyl, *tert*-butoxycarbonyl, amino, methylamino, 1,3-dimethylbutylamino, aminocarbonyl, ethylaminocarbonyl, diethylaminocarbonyl, aminosulfonyl, methylsulfonyl and methylaminocarbonylmethyl. Even further examples include isopropylamino, methylaminocarbonyl, dimethylaminocarbonyl and methylcarbonylamino.

Typical values of R^a include methyl, ethyl, isopropyl, *tert*-butyl, methoxymethyl, acetylaminomethyl, dimethylhydrazinylcarbonylethyl, aminocarbonylaminoethyl, 1-(methoxycarbonylmethyl)ethyl, 1-(carboxymethyl)ethyl, 3-hydroxy(1-methyl)propyl, aminocarbonylethyl, aminomethyl, methylaminomethyl, dimethylaminomethyl, (1,3-dimethylbutyl)aminomethyl, 1-(methylamino)ethyl, phenyl, methylphenyl, phenyl(methylamino)methyl, phenyl(methyl)methyl, dimethylaminophenyl, acetylaminophenyl, tetrahydrofuranyl, oxopyrrolidinyl, tetrahydropyranyl, acetylpiperidinyl, dioxoimidazolidinylmethyl, hydroxy(1-*tert*-butoxycarbonyl)-pyrrolidinyl, hydroxypyrrolidinyl, piperidinyl, ethylaminocarbonylpiperidinyl, methylsulfonylpiperidinyl, methylaminocarbonylmethylpiperidinyl, oxoimidazolidinyl, oxooxazolidinyl, oxodihydropyridazinyl, morpholinylmethyl, methylpiperazinylmethyl, acetylaminopyrrolidinylmethyl, hydroxypyrrolidinylmethyl, hydroxymethyl-

pyrrolidinylmethyl, pyrrolidinylmethyl, (hydroxymethyl)piperidinylmethyl, hydroxypiperidinylmethyl, (hydroxyethyl)piperidinylmethyl, aminocarbonyl-piperidinylmethyl, diethylaminocarbonylpiperidinylmethyl, tetrahydrothienylmethyl, furyl, methylpyrrolyl, pyridinyl, methylpyrazinyl, methylisoxazolylmethyl, imidazolyl, thienyl, thiazolyl, methylthiazolyl, dimethylpyridinonyl, methylpyrazolyl, benzimidazolyl, naphthyridinyl, cinnolinyl, pyridylmethyl, imidazolylmethyl, imidazolyl(acetylamino)ethyl, benzotriazolylmethyl, benzimidazoylethyl, cyclopropyl, cyclopentyl, hydroxycyclopentyl, oxocyclopentyl, hydroxycyclohexyl and methoxycyclohexyl. Further typical examples include 2-aminocarbonyl-1-methylethyl, 2-(dimethylaminocarbonyl)-1-methylethyl, 2-(methylaminocarbonyl)-1-methylethyl, 1-methylcarbonylamino-2-hydroxyethyl, isopropylaminomethyl, isobutyl, methylpiperidinyl, dioxotetrahydrothienylmethyl, acetylpyrrolidinyl, *tert*-butoxycarbonylazetidinyl, azetidinyl, *tert*-butoxycarbonylpyrrolidinyl, pyrrolidinyl, acetylpyrrolidinyl, aminocarbonylpyrrolidinylmethyl, oxopiperazinylmethyl, hydroxy(1-acetyl)pyrrolidinyl, hydroxyazetidinylmethyl, methylaminocarbonylmethylazetidinyl, methylaminocarbonylmethylpyrolidinyl, dimethylmorpholinylmethyl, hydroxypiperidinylmethyl, methylimidazolyl, tetrazolylmethyl, imidazolylmethyl and methylisoxazolylmethyl.

In one group of compounds, typical values of R^a include methyl, methoxymethyl, acetylaminomethyl, dimethylhydrazinylcarbonylethyl, aminocarbonylaminoethyl, dimethylaminophenyl, acetylaminophenyl, tetrahydrofuranyl, oxopyrrolidinyl, tetrahydropyranyl, acetylpiperidinyl, dioxoimidazolidinylmethyl, furyl, methylpyrrolyl, pyridinyl, methylpyrazinyl and methylisoxazolylmethyl.

In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents C_{1-6} alkyl, especially methyl, ethyl or *tert*-butyl.

In one group of compounds, R^c suitably represents hydrogen; or C_{1-6} alkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl, either of which groups may be optionally substituted by one or more substituents.

Examples of typical substituents on R^c include C_{1-6} alkyl, carboxy, C_{2-6} alkoxycarbonyl and di(C_{1-6})alkylamino. Further typical examples include oxo, halogen, hydroxy, hydroxy(C_{1-6})alkyl and aminosulfonyl. More typical examples include C_{2-6} alkylcarbonylamino, aminocarbonyl and phenyl.

Examples of particular substituents on R^c include methyl, carboxy, ethoxycarbonyl and dimethylamino. More examples of particular substituents on R^c include oxo, fluoro, hydroxy, hydroxymethyl and aminosulfonyl. Further examples of particular substituents on R^c include methoxycarbonyl, *tert*-butoxycarbonyl, acetylamino, aminocarbonyl and phenyl.

Typical values of R^c include hydrogen, methyl, carboxymethyl, ethoxycarbonyl-methyl, ethyl, ethoxycarbonylethyl, dimethylaminoethyl and methylpiperazinylpropyl, acetyl, tetrahydropyranylcarbonyl, piperidinyl, piperidinylethyl, pyrrolidinylmethyl, methylpyrrolidinylmethyl, morpholinylethyl, morpholinyl(dimethyl)ethyl, 1,1-dioxidotetrahydrothienyl, 1,1-dioxidothiomorpholinylethyl, aminosulfonylphenyl, fluorophenyl, phenyl(hydroxy)ethyl, thiazolyl, pyridinyl, pyrimidinyl, methylimidazolylmethyl, imidazolylpropyl, pyridinylmethyl, indolylethyl, cyclopropylmethyl, hydroxymethylcyclopentyl, cyclohexyl, hydroxycyclohexyl and hydroxycyclohexylmethyl. Further typical values of R^c include isopropyl, *tert*-butyl, 2-methylbutyl, acetylaminoethyl, 1-carboxypropyl, phenyl(hydroxy)propyl, aminocarbonylmethyl, 2-hydroxy-1-methoxycarbonylethyl, methylpiperidinyl, cyclopropyl, tetrahydrofuranyl, oxotetrahydrofuranyl, tetrahydropyranyl, *tert*-butoxycarbonylazetidinyl, azetidinyl, *tert*-butoxycarbonylpiperidinyl, thienyl, methyltriazolylmethyl and dimethylpyrazolylmethyl.

In one group of compounds, typical values of R^c include hydrogen, methyl, carboxymethyl, ethoxycarbonyl-methyl, ethyl, ethoxycarbonylethyl, dimethylaminoethyl and methylpiperazinylpropyl.

In one embodiment, R^d represents hydrogen. In another embodiment, R^d represents C_{1-6} alkyl, especially methyl. In another embodiment, R^d represents hydroxy(C_{1-6})alkyl. Representative hydroxy(C_{1-6})alkyl groups include 2-hydroxyethyl, 2-hydroxyprop-1-yl, 3-hydroxypropyl, 4-hydroxybutyl, 1-hydroxyprop-2-yl, 1-hydroxy-4-methylpent-2-yl, 1-hydroxybut-2-yl, 1-hydroxy-2-methylprop-2-yl, 1-hydroxy-3-methylbut-2-yl, 2-hydroxybut-1-yl and 3-hydroxy-2-dimethylprop-1-yl. Further representative hydroxy(C_{1-6})alkyl groups include 4-hydroxypentyl, 1-hydroxy-3-methylpent-2-yl and 6-hydroxyhexyl.

Alternatively, the moiety $-NR^cR^d$ may suitably represent azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl or piperazin-1-yl, any of which groups may be optionally substituted by C_{1-6} alkyl (e.g. methyl). The moiety $-NR^cR^d$ may

also be substituted by hydroxy. Particular values of $-NR^cR^d$ include morpholin-4-yl and 4-methylpiperazin-1-yl. Further values include azetidin-1-yl and hydroxy-pyrrolidin-1-yl.

Suitably, R^e represents C_{1-6} alkyl; or R^e represents aryl, optionally substituted by C_{1-6} alkyl. R^e also suitably represents heteroaryl or heteroaryl(C_{1-6})alkyl.

In one embodiment, R^e represents C_{1-6} alkyl, typically methyl, isopropyl or *n*-propyl, especially *n*-propyl. In another embodiment, R^e represents aryl, optionally substituted by C_{1-6} alkyl; examples include phenyl and methylphenyl (especially 4-methylphenyl). In a further embodiment, R^e represents heteroaryl, optionally substituted by C_{1-6} alkyl, typically methylimidazolyl (especially 1-methylimidazol-4-yl). In a still further embodiment, R^e represents heteroaryl(C_{1-6})alkyl, typically pyridinylmethyl, especially pyridin-2-ylmethyl or pyridin-4-ylmethyl.

Typically, Z represents hydrogen, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-COCO_2R^b$, $-COCONR^cR^d$, $-COCH_2NR^cR^d$, $-COCH_2NR^cCONR^cR^d$, $-COCH_2NR^cCO_2R^b$, $-NR^cCOR^a$, $-SO_2R^e$ or $-SO_2NHCO_2R^b$; or Z represents an optionally substituted phenyl, heteroaryl or C_{3-7} heterocycloalkyl group.

In one group of compounds Z typically represents hydrogen, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-NR^cCOR^a$, $-SO_2R^e$ or $-SO_2NHCO_2R^b$; or Z represents an optionally substituted heteroaryl group.

Suitable heteroaryl groups that may represent the group Z include imidazolyl, oxadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, thiazolyl and isoxazolyl, more suitably imidazolyl (especially 1*H*-imidazol-2-yl or 1*H*-imidazol-4-yl). Typical substituents that may be present on the Z heteroaryl group include methyl, cyano, amino and nitro. Illustrative examples include 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, oxadiazol-3-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 5-aminopyridin-2-yl, 5-cyanopyridin-2-yl, 5-methylisoxazol-3-yl, pyrimidin-2-yl, pyrazin-2-yl and 5-nitrothiazol-2-yl. A further example includes pyridin-2-yl-N-oxide.

When Z is an optionally substituted C_{3-7} heterocycloalkyl group, suitable examples include optionally substituted tetrahydrofuranyl and piperidinyl. Typical substituents include tert-butoxycarbonyl and oxo. Representative examples for C_{3-7} heterocycloalkyl group that may represent Z include tetrahydrofuran-3-yl, 2-oxotetrahydrofuran-3-yl, piperidin-4-yl and 1-*tert*-butoxycarbonylpiperidin-4-yl.

Suitably, Z represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-SO_2NHCO_2R^b$ or $-COCH_2NR^cR^d$. In one group of compounds Z represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, -

$CONR^cOR^b$ or $-SO_2NHCO_2R^b$. In one particular group of compounds of the invention Z represents $-CONR^cR^d$ or $-COCH_2NR^cR^d$.

Selected values of Z include hydrogen, acetyl, methoxyacetyl, acetylamino-methylcarbonyl, dimethylhydrazinylcarbonylethylcarbonyl, aminocarbonylamino-ethylcarbonyl, ethylcarbonyl, isopropylcarbonyl, *tert*-butylcarbonyl, 1-(methoxycarbonylmethyl)ethyl-1-carbonyl, 1-(carboxymethyl)ethyl-1-carbonyl, 3-hydroxy(1-methyl)propyl-1-carbonyl, aminocarbonylethylcarbonyl, aminomethylcarbonyl, methylaminomethylcarbonyl, dimethylaminomethylcarbonyl, (1,3-dimethylbutyl)-aminomethylcarbonyl, 1-(methylamino)ethyl-1-carbonyl, dimethylaminophenylcarbonyl, acetylaminophenylcarbonyl, phenylcarbonyl, methylphenylcarbonyl, phenyl(methylamino)methylcarbonyl, phenyl(methyl)methylcarbonyl, tetrahydrofuranylcarbonyl, oxopyrrolidinylcarbonyl, tetrahydropyranylcarbonyl, acetylpiperidinylcarbonyl, dioxoimidazolidinylmethylcarbonyl, hydroxy(1-*tert*-butoxycarbonyl)pyrrolidinylcarbonyl, hydroxypyrrolidinylcarbonyl, piperidinylcarbonyl, ethylaminocarbonylpiperidinylcarbonyl, methylsulfonylpiperidinylcarbonyl, methylaminocarbonylmethylpiperidinylcarbonyl, oxoimidazolidinylcarbonyl, oxooxazolidinylcarbonyl, oxodihydropyridazinylcarbonyl, morpholinylmethylcarbonyl, methylpiperazinylmethylcarbonyl, acetylaminopyrrolidinylmethylcarbonyl, hydroxypyrrolidinylmethylcarbonyl, hydroxymethylpyrrolidinylmethylcarbonyl, pyrrolidinylmethylcarbonyl, (hydroxymethyl)piperidinylmethylcarbonyl, hydroxypiperidinylmethylcarbonyl, (hydroxyethyl)piperidinylmethylcarbonyl, aminocarbonylpiperidinylmethylcarbonyl, diethylaminocarbonyl-piperidinylmethylcarbonyl, tetrahydrothienylmethylcarbonyl, furylcarbonyl, methylpyrrolylcarbonyl, pyridinylcarbonyl, methylpyrazinylcarbonyl, methylisoxazolyl-methylcarbonyl, imidazolylcarbonyl, thienylcarbonyl, thiazolylcarbonyl, methylthiazolylcarbonyl, dimethylpyridinonylcarbonyl, methylpyrazolylcarbonyl, benzimidazolylcarbonyl, naphthyridinylcarbonyl, cinnolinylcarbonyl, pyridylmethylcarbonyl, imidazolylmethylcarbonyl, imidazolyl(acetylamino)ethylcarbonyl, benzotriazolyl-methylcarbonyl, benzimidazoylethylcarbonyl, cyclopropylcarbonyl, cyclopentylcarbonyl, hydroxycyclopentylcarbonyl, oxocyclopentylcarbonyl, hydroxycyclohexylcarbonyl, methoxycyclohexylcarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, carboxyl, methoxycarbonyl, aminocarbonyl, methylamino-carbonyl, carboxymethylaminocarbonyl, ethoxycarbonylmethylaminocarbonyl, ethylaminocarbonyl,

ethoxycarbonyl-ethylaminocarbonyl, (dimethylamino)ethyl-aminocarbonyl, methylpiperazinyl-propylaminocarbonyl, dimethylaminocarbonyl, morpholinylethylaminocarbonyl, pyridinylmethylaminocarbonyl, 1,1-dioxidotetrahydrothienyl-aminocarbonyl, 1,1-dioxidothiomorpholinylethyl-aminocarbonyl, piperidinylaminocarbonyl, piperidinylethylaminocarbonyl, fluorophenylaminocarbonyl, thiazolylaminocarbonyl, imidazolylpropylaminocarbonyl, (methylimidazolylmethyl)(methyl)aminocarbonyl, indolylethylaminocarbonyl, pyrimidinylaminocarbonyl, pyridinylaminocarbonyl, pyridinylmethylaminocarbonyl, cyclopropylmethylaminocarbonyl, morpholin-4-ylcarbonyl, methylpiperazin-1-ylcarbonyl, methoxyaminocarbonyl, *N*-methoxy-*N*-methylaminocarbonyl, acetylamino, propylsulfonyl, methylsulfonyl, pyridinylmethylsulfonyl, methylimidazolylsulfonyl, *tert*-butoxycarbonylaminosulphonyl, imidazolyl, oxadiazolyl, pyridinyl, aminopyridinyl, cyanopyridinyl, methylisoxazolyl, pyrimidinyl, pyrazinyl, nitrothiazolyl, hydroxyoxalyl, methoxyoxalyl, ethoxyoxalyl, methyloxamoyl, dimethyloxamoyl, pyridinylaminomethylcarbonyl, hydroxycyclohexyl-aminomethylcarbonyl, cyclohexyl(hydroxyethyl)aminomethylcarbonyl, hydroxypropyl-aminomethylcarbonyl, hydroxy(methyl)propylaminomethylcarbonyl, hydroxybutyl-aminomethylcarbonyl, hydroxy(methyl)butylaminomethylcarbonyl, hydroxy(methyl)-pentylaminomethylcarbonyl, hydroxymethylcyclopentylaminomethylcarbonyl, phenyl(hydroxy)ethylaminomethylcarbonyl, hydroxycyclohexylmethyl-aminomethylcarbonyl, indolylethylaminomethylcarbonyl, pyrimidinylamino-methylcarbonyl, morpholinylethylaminomethylcarbonyl, morpholinyl(dimethyl)-ethylaminomethylcarbonyl, methylimidazolylmethylaminomethylcarbonyl, aminosulfonylphenylaminomethylcarbonyl, pyrrolidinylmethylaminomethylcarbonyl, methylpyrrolidinylmethylaminomethylcarbonyl, thiazolylaminomethylcarbonyl, acetylaminomethylcarbonyl, tetrahydropyranylcarbonylaminomethylcarbonyl, phenyl, tetrahydrofuranyl, oxotetrahydrofuranyl, piperidinyl, tert-butoxypiperidinyl, dimethylureamethylcarbonyl, morpholinylcarbonylaminomethylcarbonyl and *tert*-butoxycarbonyl(methyl)aminomethylcarbonyl. Further selected values of Z include 2-aminocarbonyl-1-methylethylcarbonyl, 2-(dimethylaminocarbonyl)-1-methylethylcarbonyl, 2-(methylaminocarbonyl)-1-methylethylcarbonyl, 1-methylcarbonylamino-2-hydroxyethylcarbonyl, isopropylaminomethylcarbonyl, isobutylcarbonyl, methylpiperidinylcarbonyl, azetidin-1-ylcarbonyl, hydroxy-pyrrolidin-1-

ylcarbonyl, dioxotetrahydrothienylmethylcarbonyl, acetylpyrrolidinylcarbonyl, *tert*-butoxycarbonylazetidinylcarbonyl, azetidinylcarbonyl, *tert*-butoxycarbonyl-pyrrolidinylcarbonyl, pyrrolidinylcarbonyl, acetylpyrrolidinylcarbonyl, aminocarbonylpyrrolidinylmethylcarbonyl, oxopiperazinylmethylcarbonyl, hydroxy(1-acetyl)pyrrolidinylcarbonyl, hydroxyazetidinylmethylcarbonyl, methylaminocarbonyl-methylazetidinylcarbonyl, methylaminocarbonylmethylpyrolidinylcarbonyl, dimethylmorpholinylmethylcarbonyl, hydroxypiperidinylmethylcarbonyl, methylimidazolylcarbonyl, tetrazolylmethylcarbonyl, imidazolylmethylcarbonyl, methylisoxazolylmethylcarbonyl, pyridin-2-yl-N-oxide, isopropylaminocarbonyl, methylpiperidinylaminocarbonyl, cyclopropylaminocarbonyl, tetrahydropyranylaminocarbonyl, azetidinylaminocarbonyl, *tert*-butoxycarbonyl-piperidinylaminocarbonyl, thienylaminocarbonyl, *tert*-butyl(hydroxyethyl)-aminomethylcarbonyl, 2-methylbutyl(hydroxyethyl) aminomethylcarbonyl, tetrahydropyranylacetyl(methyl)aminomethylcarbonyl, tetrahydrofuranyl-aminomethylcarbonyl, oxotetrahydrofuranylaminomethylcarbonyl, *tert*-butoxycarbonylazetidinylaminomethylcarbonyl, azetidinylaminomethylcarbonyl, 1-carboxypropylaminomethylcarbonyl, ethyl(hydroxyethyl)aminomethylcarbonyl, acetylaminoethylaminomethylcarbonyl, phenyl(hydroxy)propylaminomethylcarbonyl, hydroxycyclohexylaminomethylcarbonyl, ethyl(4-hydroxybutyl)aminomethylcarbonyl, 2-hydroxy-1-methoxycarbonylethylaminomethylcarbonyl, aminocarbonylmethyl-(methyl)aminomethylcarbonyl, 6-hydroxyhexylaminomethylcarbonyl, methyltriazolylmethylaminomethylcarbonyl, dimethylpyrazolyl-methyl(methyl)aminomethylcarbonyl, dimethylaminocarbonyl(methyl)-aminomethylcarbonyl and 1-hydroxy-3-methylpent-2-ylaminomethylcarbonyl.

In one group of compounds selected values of Z include hydrogen, acetyl, methoxyacetyl, acetylamino-methylcarbonyl, dimethylhydrazinylcarbonylethylcarbonyl, aminocarbonylamino-ethylcarbonyl, dimethylaminophenylcarbonyl, acetylaminophenylcarbonyl, tetrahydrofuranylcarbonyl, oxopyrrolidinylcarbonyl, tetrahydropyranylcarbonyl, acetylpiperidinylcarbonyl, dioxoimidazolidinylmethylcarbonyl, furylcarbonyl, methylpyrrolylcarbonyl, pyridinylcarbonyl, methylpyrazinylcarbonyl, methylisoxazolyl-methylcarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylamino-carbonyl, carboxymethylaminocarbonyl, ethoxycarbonylmethylaminocarbonyl, ethylaminocarbonyl,

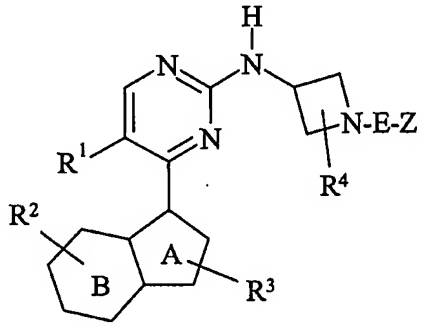
ethoxycarbonylethylaminocarbonyl, (dimethylamino)ethyl-aminocarbonyl, methylpiperazinylpropylaminocarbonyl, dimethylaminocarbonyl, morpholin-4-ylcarbonyl, methoxyaminocarbonyl, *N*-methoxy-*N*-methylaminocarbonyl, acetylamino, propylsulphonyl, *tert*-butoxycarbonylaminosulphonyl and imidazolyl.

Suitable values of R^3 include hydrogen, methylaminocarbonylmethyl, phenylsulphonyl and methylphenylsulphonyl (especially 4-methylphenylsulphonyl). R^3 may also suitably represent C_{1-6} alkyl, typically methyl. Preferably, R^3 is hydrogen.

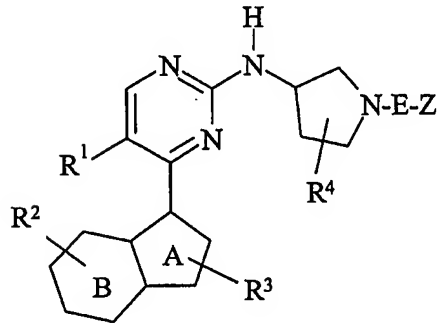
Typical values of R^4 include hydrogen, methoxy, oxo, methoxycarbonyl, aminocarbonyl and dimethylaminocarbonyl.

Suitably, R^4 represents hydrogen or C_{1-6} alkoxy. Particular values of R^4 include hydrogen and methoxy. Preferably, R^4 is hydrogen.

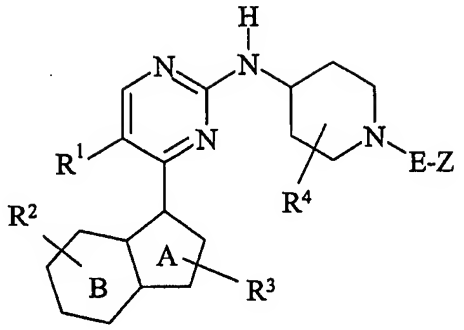
A typical sub-class of compounds in accordance with the invention is represented by the compounds of formula (IA), (IB) and (IC) and (ICi), especially (IC) and (ICi):



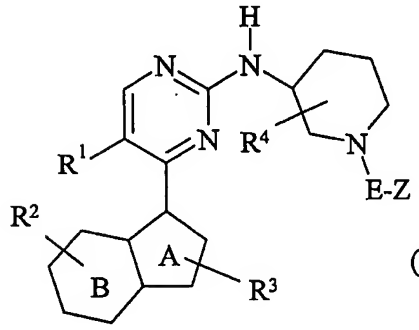
(IA)



(IB)



(IC)

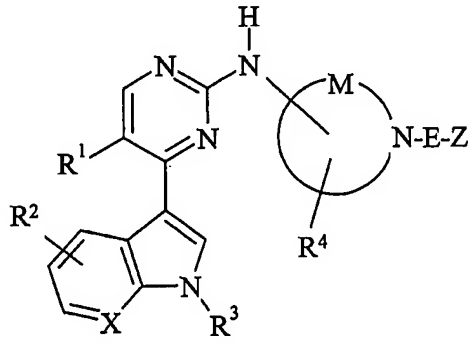


(ICi)

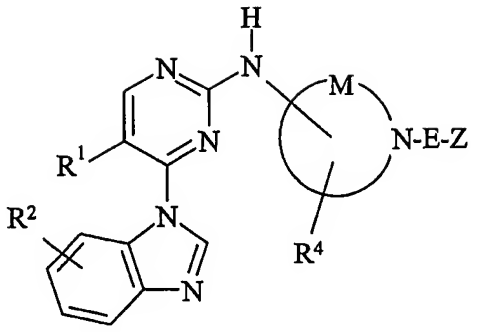
wherein A, B, R^1, R^2, R^3, R^4, E and Z are as defined above.

In one group of compounds a typical sub-class in accordance with the invention is represented by the compounds of formula (IA), (IB) and (IC) especially (IC).

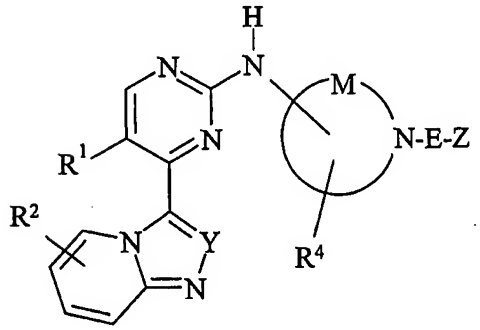
Another sub-class of compounds in accordance with the invention is represented by the compounds of formula (ID), (IE), (IF), (IG), (IH), (IJ), (IK), (IL), (IM), especially (ID):



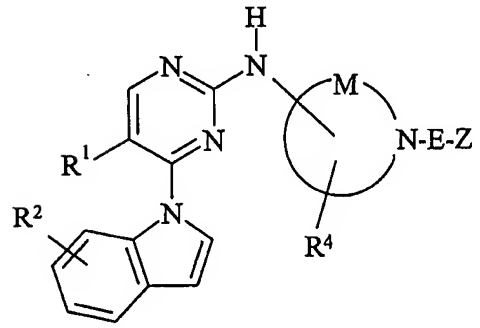
(ID)



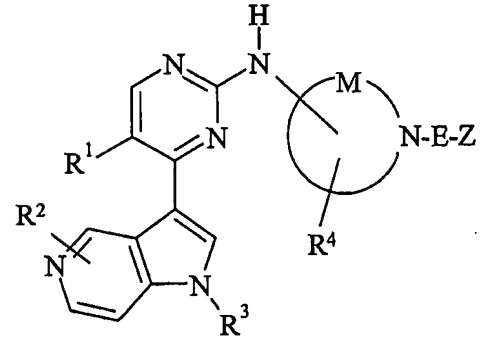
(IE)



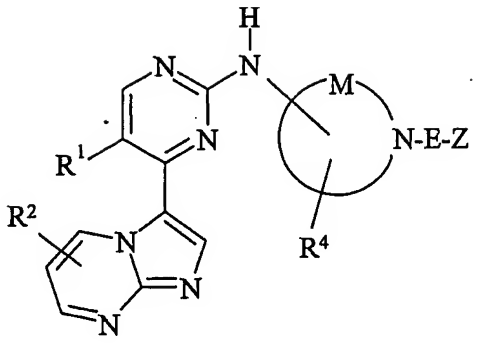
(IF)



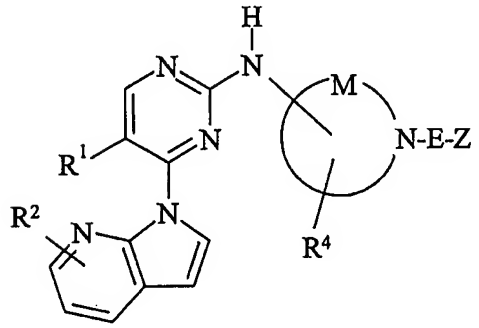
(IG)



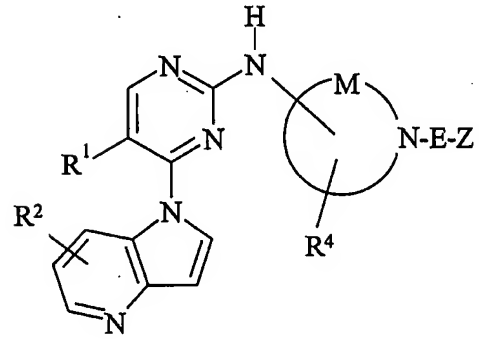
(IH)



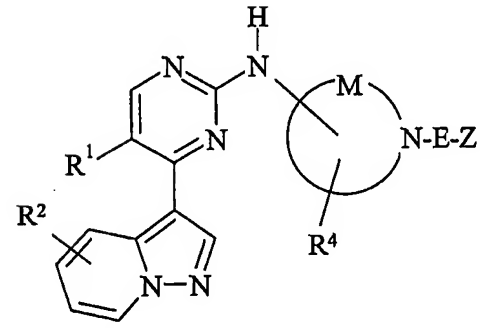
(IJ)



(IK)



(IL)



(IM)

wherein X represents CH or N;

Y represents CH or N; and

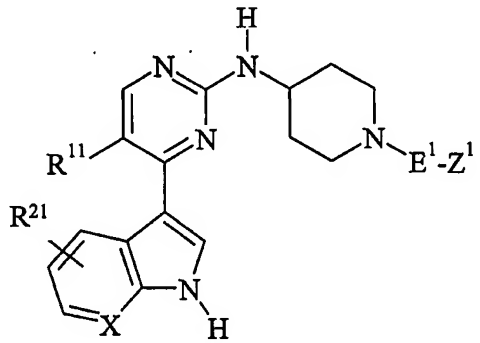
R^1, R^2, R^3, R^4, M, E and Z are as defined above.

In one embodiment, X is CH. In another embodiment, X is N.

In one embodiment, Y is CH. In another embodiment, Y is N.

One sub-class of compounds in accordance with the invention is represented by the compounds of formula (ID), (IE), (IF), (IG), (IH), (IJ), (IK) and (IL). Another sub-class of compounds in accordance with the invention is represented by the compounds of formula (ID), (IE), (IF), (IG), (IH), (IJ), especially (ID). Another sub-class of compounds in accordance with the invention is represented by the compounds of formula (ID), (IE) and (IF). One particular sub-class is represented by a compound of formula (ID). Another particular sub-class is represented by a compound of formula (IF), especially when Y is CH.

A particular sub-group of compounds according to the invention is represented by the compounds of formula (II):



(II)

wherein

R^{11} represents hydrogen, halogen, cyano or C_{1-6} alkyl;

R^{21} represents hydrogen, halogen or cyano;

E^1 represents a covalent bond or a methylene linkage;

Z^1 represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-SO_2NHCO_2R^b$ or $-COCH_2NR^cR^d$;

and

R^a, R^b, R^c, R^d and X are as defined above.

Particular values of R^{11} include hydrogen, fluoro, chloro, cyano and methyl.

Suitably, R^{11} represents hydrogen, halogen or C_{1-6} alkyl, especially hydrogen or halogen.

Typically, R^{11} represents halogen or cyano.

In one embodiment, R^{11} represents hydrogen. In another embodiment, R^{11} represents halogen, in particular fluoro or chloro, especially chloro. In an additional embodiment, R^{11} represents cyano. In a further embodiment, R^{11} represents C_{1-6} alkyl, in particular methyl or ethyl, especially methyl.

Typically R^{21} represents hydrogen or halogen. Particular values of R^{21} include hydrogen and fluoro. Further, R^{21} may also in particular represent chloro.

In one embodiment, R^{21} represents hydrogen. In another embodiment, R^{21} represents halogen, in particular fluoro or chloro. In one embodiment R^{21} represents fluoro.

In one embodiment, E^1 represents a covalent bond. In another embodiment, E^1 represents a methylene linkage.

In one group of compounds of formula (II) Z^1 represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$ or $-SO_2NHCO_2R^b$. In one particular group of compounds of formula (II) Z^1 represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$ or $-COCH_2NR^cR^d$. In another particular group of compounds Z^1 represents $-CONR^cR^d$ or $-COCH_2NR^cR^d$.

Particular values of Z^1 include acetyl, methoxyacetyl, acetylamino-methylcarbonyl, dimethylhydrazinylcarbonylethylcarbonyl, aminocarbonylamino-ethylcarbonyl, ethylcarbonyl, isopropylcarbonyl, *tert*-butylcarbonyl, 1-(methoxycarbonylmethyl)ethyl-1-carbonyl, 1-(carboxymethyl)ethyl-1-carbonyl, 3-hydroxy(1-methyl)propyl-1-carbonyl, aminocarbonylethylcarbonyl, aminomethylcarbonyl, methylaminomethylcarbonyl, dimethylaminomethylcarbonyl, (1,3-dimethylbutyl)aminomethylcarbonyl, 1-(methylamino)ethyl-1-carbonyl, dimethylaminophenylcarbonyl, acetylaminophenylcarbonyl, phenylcarbonyl, methylphenylcarbonyl, phenyl(methylamino)methylcarbonyl, phenyl(methyl)methylcarbonyl, tetrahydrofuranylcarbonyl, oxopyrrolidinylcarbonyl, tetrahydropyranylcarbonyl, acetylpiperidinylcarbonyl, dioxoimidazolidinylmethylcarbonyl, hydroxy(1-*tert*-butoxycarbonyl)pyrrolidinylcarbonyl, hydroxypyrrolidinylcarbonyl, piperidinylcarbonyl, ethylaminocarbonyl-piperidinylcarbonyl, methylsulfonylpiperidinylcarbonyl, methylaminocarbonylmethylpiperidinylcarbonyl, oxoimidazolidinylcarbonyl, oxooxazolidinylcarbonyl, oxodihydropyridazinylcarbonyl, morpholinylmethylcarbonyl, methylpiperazinylmethylcarbonyl, acetylaminopyrrolidinylmethylcarbonyl, hydroxypyrrolidinylmethylcarbonyl, hydroxymethylpyrrolidinylmethylcarbonyl,

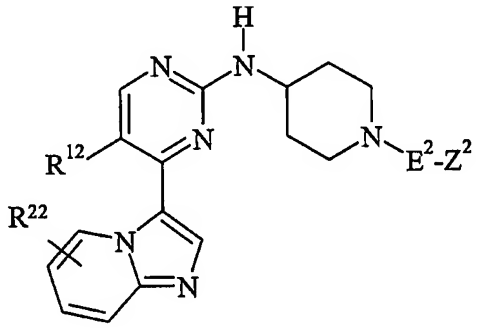
pyrrolidinylmethylcarbonyl, (hydroxymethyl)piperidinylmethylcarbonyl, hydroxypiperidinylmethylcarbonyl, (hydroxyethyl)piperidinylmethylcarbonyl, aminocarbonylpiperidinylmethylcarbonyl, diethylaminocarbonylpiperidinyl-methylcarbonyl, tetrahydrothienylmethylcarbonyl, furylcarbonyl, methylpyrrolylcarbonyl, pyridinylcarbonyl, methylpyrazinylcarbonyl, methylisoxazolyl-methylcarbonyl, imidazolylcarbonyl, thienylcarbonyl, thiazolylcarbonyl, methylthiazolylcarbonyl, dimethylpyridinonylcarbonyl, methylpyrazolylcarbonyl, benzimidazolylcarbonyl, naphthyridinylcarbonyl, cinnolinylcarbonyl, pyridylmethylcarbonyl, imidazolylmethylcarbonyl, imidazolyl(acetylamino)ethylcarbonyl, benzotriazolylmethylcarbonyl, benzimidazoylethylcarbonyl, cyclopropylcarbonyl, cyclopentylcarbonyl, hydroxycyclopentylcarbonyl, oxocyclopentylcarbonyl, hydroxycyclohexylcarbonyl, methoxycyclohexylcarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, carboxyl, methoxycarbonyl, aminocarbonyl, methylamino-carbonyl, carboxymethylaminocarbonyl, ethoxycarbonylmethylaminocarbonyl, ethylaminocarbonyl, ethoxycarbonylethylaminocarbonyl, (dimethylamino)ethyl-aminocarbonyl, methylpiperazinylpropylaminocarbonyl, dimethylaminocarbonyl, morpholinylethylaminocarbonyl, pyridinylmethylaminocarbonyl, 1,1-dioxidotetrahydrothienyl-aminocarbonyl, 1,1-dioxidothiomorpholinylethyl-aminocarbonyl, piperidinylaminocarbonyl, piperidinylethylaminocarbonyl, fluorophenylaminocarbonyl, thiazolylaminocarbonyl, imidazolylpropylaminocarbonyl, (methylimidazolylmethyl)(methyl)aminocarbonyl, indolylethylaminocarbonyl, pyrimidinylaminocarbonyl, pyridinylaminocarbonyl, pyridinylmethylaminocarbonyl, cyclopropylmethylaminocarbonyl, morpholin-4-ylcarbonyl, methylpiperazin-1-ylcarbonyl, methoxyaminocarbonyl, *N*-methoxy-*N*-methylaminocarbonyl, *tert*-butoxycarbonylaminosulphonyl, pyridinylaminomethylcarbonyl, hydroxycyclohexylaminomethylcarbonyl, cyclohexyl(hydroxyethyl)aminomethylcarbonyl, hydroxypropylaminomethylcarbonyl, hydroxy(methyl)propylaminomethylcarbonyl, hydroxybutylaminomethylcarbonyl, hydroxy(methyl)butylaminomethylcarbonyl, hydroxy(methyl)pentylaminomethylcarbonyl, hydroxymethylcyclopentyl-aminomethylcarbonyl, phenyl(hydroxy)ethylaminomethylcarbonyl, hydroxycyclohexylmethylaminomethylcarbonyl, indolylethylaminomethylcarbonyl, pyrimidinylaminomethylcarbonyl, morpholinylethylaminomethylcarbonyl, morpholinyl(dimethyl)ethylaminomethylcarbonyl, methylimidazolylmethyl-

aminomethylcarbonyl, aminosulfonylphenylaminomethylcarbonyl, pyrrolidinylmethylaminomethylcarbonyl, methylpyrrolidinylmethylaminomethylcarbonyl, thiazolylaminomethylcarbonyl, acetylaminomethylcarbonyl and tetrahydropyranylcarbonylaminomethylcarbonyl. Further particular values of Z^1 include 2-aminocarbonyl-1-methylethylcarbonyl, 2-(dimethylaminocarbonyl)-1-methylethylcarbonyl, 2-(methylaminocarbonyl)-1-methylethylcarbonyl, 1-methylcarbonylamino-2-hydroxyethylcarbonyl, isopropylaminomethylcarbonyl, isobutylcarbonyl, methylpiperidinylcarbonyl, azetidin-1-ylcarbonyl, hydroxy-pyrrolidin-1-ylcarbonyl, dioxotetrahydrothienylmethylcarbonyl, acetylpyrrolidinylcarbonyl, *tert*-butoxycarbonylazetidinylcarbonyl, azetidinylcarbonyl, *tert*-butoxycarbonyl-pyrrolidinylcarbonyl, pyrrolidinylcarbonyl, acetylpyrrolidinylcarbonyl, aminocarbonylpyrrolidinylmethylcarbonyl, oxopiperazinylmethylcarbonyl, hydroxy(1-acetyl)pyrrolidinylcarbonyl, hydroxyazetidinylmethylcarbonyl, methylaminocarbonylmethylazetidinylcarbonyl, methylaminocarbonyl-methylpyrolidinylcarbonyl, dimethylmorpholinylmethylcarbonyl, hydroxypiperidinylmethylcarbonyl, methylimidazolylcarbonyl, tetrazolylmethylcarbonyl, imidazolylmethylcarbonyl, methylisoxazolylmethylcarbonyl, isopropylaminocarbonyl, methylpiperidinylaminocarbonyl, cyclopropylaminocarbonyl, tetrahydropyranylaminocarbonyl, azetidinylaminocarbonyl, *tert*-butoxycarbonyl-piperidinylaminocarbonyl, thienylaminocarbonyl, *tert*-butyl(hydroxyethyl)-aminomethylcarbonyl, 2-methylbutyl(hydroxyethyl) aminomethylcarbonyl, tetrahydropyranylacetyl(methyl)aminomethylcarbonyl, tetrahydrofuranylaminomethylcarbonyl, oxotetrahydrofuranylaminomethylcarbonyl, *tert*-butoxycarbonylazetidinylaminomethylcarbonyl, azetidinylaminomethylcarbonyl, 1-carboxypropylaminomethylcarbonyl, ethyl(hydroxyethyl)aminomethylcarbonyl, acetylaminoethylaminomethylcarbonyl, phenyl(hydroxy)propylaminomethylcarbonyl, hydroxycyclohexylaminomethylcarbonyl, ethyl(4-hydroxybutyl)aminomethylcarbonyl, 2-hydroxy-1-methoxycarbonylethylaminomethylcarbonyl, aminocarbonylmethyl-(methyl)aminomethylcarbonyl, 6-hydroxyhexylaminomethylcarbonyl, methyltriazolylmethylaminomethylcarbonyl, dimethylpyrazolylmethyl-(methyl)aminomethylcarbonyl, dimethylaminocarbonyl(methyl)aminomethylcarbonyl and 1-hydroxy-3-methylpent-2-ylaminomethylcarbonyl.

In one group of compounds selected values of Z^1 include acetyl, methoxyacetyl, acetylaminomethylcarbonyl, dimethylhydrazinylcarbonylethylcarbonyl, aminocarbonylaminoethylcarbonyl, dimethylaminophenylcarbonyl, acetylaminophenylcarbonyl, tetrahydrofuranylcarbonyl, oxopyrrolidinylcarbonyl, tetrahydropyranylcarbonyl, acetylpiperidinylcarbonyl, dioxoimidazolidinylmethylcarbonyl, furylcarbonyl, methylpyrrolylcarbonyl, pyridinylcarbonyl, methylpyrazinylcarbonyl, methylisoxazolylmethylcarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl, aminocarbonyl, methylaminocarbonyl, ethylaminocarbonyl, dimethylaminocarbonyl, morpholin-4-ylcarbonyl, (dimethylamino)ethylaminocarbonyl, methylpiperazinylpropylaminocarbonyl, methoxyaminocarbonyl, *N*-methoxy-*N*-methylaminocarbonyl and *tert*-butoxycarbonylaminosulphonyl.

In one particular group of compounds of the invention Z^1 represents methylaminomethylcarbonyl, dimethylaminomethylcarbonyl, (dimethylamino)ethylaminocarbonyl or piperidinylaminocarbonyl, typically piperidin-3-ylaminocarbonyl.

Another particular sub-group of compounds according to the invention is represented by the compounds of formula (IIA):



(IIA)

wherein

R^{12} represents hydrogen, halogen or C_{1-6} alkyl;

R^{22} represents hydrogen or halogen;

E^2 represents a covalent bond or a methylene linkage;

Z^2 represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, SO_2R^e or $-COCH_2NR^cR^d$; and

R^a, R^b, R^c, R^d and R^e are as defined above.

Particular values of R^{12} include hydrogen, chloro and methyl.

Suitably, R^{12} hydrogen or halogen.

In one embodiment, R^{12} represents hydrogen. In another embodiment, R^{12} represents halogen, in particular fluoro or chloro, especially chloro. In a further embodiment, R^{12} represents C_{1-6} alkyl, in particular methyl or ethyl, especially methyl.

Typically R^{22} represents hydrogen.

In one embodiment, E^2 represents a covalent bond. In another embodiment, E^2 represents a methylene linkage.

In one particular group of compounds Z^2 represents $-CONR^cR^d$.

Particular values of Z^2 include tetrahydrofuranylcarbonyl, tetrahydropyranylcarbonyl, oxopyrrolidinylcarbonyl, *tert*-butoxycarbonyl, methylaminocarbonyl, ethylaminocarbonyl, methylpiperazinylcarbonyl, methylsulfonyl, isopropylsulfonyl, methylimidazolylcarbonyl and methylcarbonylaminomethylcarbonyl. Further particular values of Z^2 include furanylcarbonyl, oxooxazolidinylcarbonyl, morpholinylmethylcarbonyl, methylisoxazolylmethylcarbonyl, isobutylcarbonyl, dimethylaminomethylcarbonyl, acetylaminomethylcarbonyl, thienylaminocarbonyl, imidazolylmethylcarbonyl, ethoxycarbonyl and dimethylaminocarbonyl.

In one particular group of compounds of formula (IIA) Z^2 represents methylaminocarbonyl or methylimidazolylcarbonyl.

Particularly useful compounds in accordance with the invention include each of the compounds described in the accompanying Examples, and pharmaceutically acceptable salts, solvates and *N*-oxides thereof.

The present invention also provides a pharmaceutical composition which comprises a compound of formula (I) as defined above, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, in association with one or more pharmaceutically acceptable carriers.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting

agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds according to the present invention may be conveniently formulated in a suitable ointment containing the active component

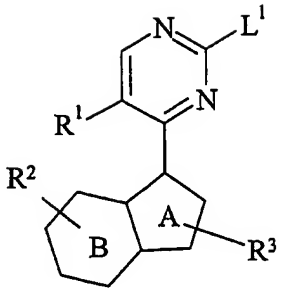
suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

For ophthalmic administration the compounds according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

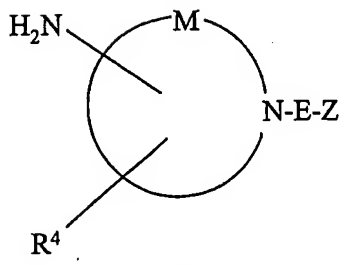
For rectal administration the compounds according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by a process which comprises reacting a compound of formula (III) with a compound of formula (IV):



(III)



(IV)

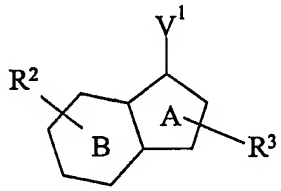
wherein A, B, M, E, Z, R^1, R^2, R^3 and R^4 are as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is typically a halogen atom, e.g. chloro; or a C_{1-6} alkylsulphonyl group, e.g. methylsulphonyl.

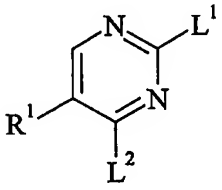
Where L^1 represents chloro, the reaction between compounds (III) and (IV) is conveniently effected at an elevated temperature in a suitable solvent, e.g. a dipolar aprotic solvent such as *N,N*-dimethylformamide, typically under basic conditions, e.g. in the presence of an inorganic base such as sodium carbonate or an organic base such as triethylamine or diisopropylethylamine.

Similarly, where L^1 represents methylsulphonyl, the reaction between compounds (III) and (IV) is conveniently effected at an elevated temperature in a suitable solvent, e.g. a lower alkanol such as ethanol or 2-ethoxyethanol, typically under basic conditions, e.g. in the presence of an organic base such as triethylamine.

The intermediates of formula (III) above may be prepared by reacting a compound of formula (V) with a compound of formula (VI):



(V)



(VI)

wherein A, B, R^1, R^2, R^3 and L^1 are as defined above, L^2 represents a suitable leaving group, and V^1 represents a boronic acid moiety $-B(OH)_2$, or V^1 represents $-ZnG^1$ in which G^1 represents a halogen atom, e.g. bromo; in the presence of a transition metal catalyst.

The leaving group L^2 is typically a halogen atom, e.g. chloro.

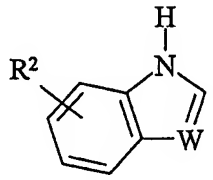
The transition metal catalyst of use in the reaction between compounds (V) and (VI) is suitably tetrakis(triphenylphosphine)palladium(0). The reaction is conveniently carried out at an elevated temperature in a solvent such as acetonitrile or tetrahydrofuran, typically in the presence of sodium carbonate.

Alternatively, the reaction between compounds (V) and (VI) may be effected in the presence of bis(dicyclohexylamino)palladium acetate (DAPCy) (*J. Org. Chem.*, 2004, **69**, 4330-4335) and potassium phosphate, typically in a lower alkanol solvent such as ethanol.

Where they are not commercially available, the starting materials of formula (V) wherein V^1 represents $-B(OH)_2$ may be prepared by the procedure described in *J. Med. Chem.*, 2001, **44**, 2229-2237, or by methods analogous thereto.

Where they are not commercially available, the starting materials of formula (V) wherein V^1 represents $-ZnG^1$ may typically be prepared *in situ* by sequential treatment of the appropriate compound of formula (V) wherein V^1 represents a halogen atom, e.g. bromo, with a base such as *n*-butyllithium and a zinc halide, e.g. zinc bromide, following the procedure described in *J. Chem. Soc., Perkin Trans. 1*, 2002, 1847-1849, or methods analogous thereto.

In an alternative procedure, the intermediates of formula (III) wherein the A/B ring system represents 1*H*-benzimidazol-1-yl or indol-1-yl may be prepared by reacting a compound of formula (VI) as defined above with a compound of formula (VII):

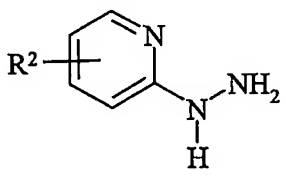


(VII)

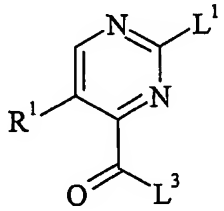
wherein R^2 is as defined above and W represents carbon or nitrogen.

The reaction is conveniently accomplished in a suitable solvent, e.g. tetrahydrofuran or *N,N*-dimethylformamide; typically under basic conditions, e.g. in the presence of an inorganic base such as sodium hydride or potassium carbonate.

In another alternative procedure, the intermediates of formula (III) wherein the A/B ring system represents [1,2,4]triazolo[4,3-*a*]pyridin-3-yl may be prepared by reacting a compound of formula (VIII) with a compound of formula (IX):



(VIII)



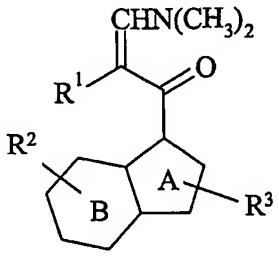
(IX)

wherein R^1, R^2 and L^1 are as defined above, and L^3 represents a suitable leaving group.

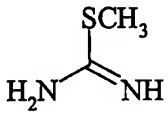
The leaving group L^3 is typically a halogen atom, e.g. chloro.

The reaction is conveniently effected under basic conditions, e.g. triethylamine in dichloromethane; followed by treatment with phosphorus oxychloride at an elevated temperature.

The intermediates of formula (III) above wherein L^1 is methylsulphonyl may be prepared from the corresponding compound wherein L^1 represents methylthio by treatment with an oxidising agent such as *meta*-chloroperbenzoic acid. The methylthio derivatives may in turn be prepared by reacting a compound of formula (X) with a compound of formula (XI) or a salt thereof, especially the sulphate salt:



(X)



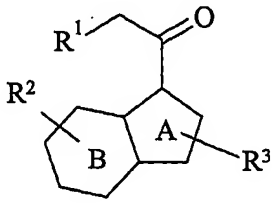
(XI)

wherein A, B, R^1, R^2 and R^3 are as defined above.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a lower alkanol such as ethanol, typically under basic conditions, e.g. in the presence of sodium ethoxide.

Alternatively, the intermediates of formula (III) wherein L^1 represents methylthio may be prepared by heating compound (X) and thiourea with a base such as sodium methoxide in a lower alkanol solvent, e.g. *n*-butanol, followed by treatment with methyl iodide, as described by Thomas *et al.* in *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2245-2248.

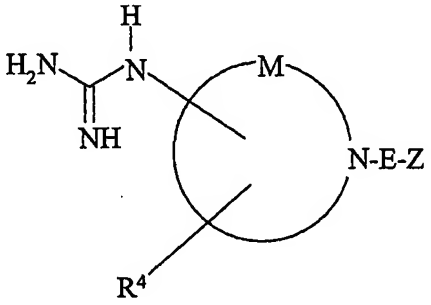
The intermediates of formula (X) above may be prepared by treating a compound of formula (XII):



(XII)

wherein A, B, R^1, R^2 and R^3 are as defined above; with the diethyl acetal of *N,N*-dimethylformamide, typically in a solvent such as tetrahydrofuran.

In an alternative process compounds of formula (I) may be prepared directly by reacting a compound (X) and a guanidine of formula (XIa):



(XIa)

Typically the reaction is heated under basic conditions e.g. in the presence of sodium hydride in an appropriate solvent such as *N,N*-dimethylformamide.

Guanidines of formula (XIa) may be prepared by treatment of the corresponding amines (IV) with a suitable reagent such as 3,5-dimethylpyrazole-1-carboxamidine nitrate.

Where they are not commercially available, the starting materials of formula (IV), (VI), (VII), (VIII), (IX), (XI) and (XII) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. By way of example, a compound of formula (I) wherein -E-Z represents *tert*-butoxycarbonyl may be converted into the corresponding compound wherein -E-Z represents hydrogen by treatment with an acid, typically trifluoroacetic acid or hydrochloric acid. A compound of formula (I) wherein -E-Z is hydrogen may be converted into the corresponding compound wherein -E-Z represents $-CONHR^c$ by reaction with the appropriate isocyanate derivative of formula $O=C=N-R^c$. Similarly, a compound of formula (I) wherein -E-Z is hydrogen may be converted into the corresponding compound wherein -E-Z represents $-CONH_2$ by treatment with trimethylsilyl isocyanate. A compound of formula (I) wherein -E-Z is hydrogen may be converted into the corresponding compound wherein -E-Z represents 1*H*-imidazol-2-ylmethyl or 1*H*-imidazol-4-ylmethyl by treatment with imidazole-2-carboxaldehyde or imidazole-4-carboxaldehyde respectively in the presence of a reducing agent, e.g. sodium cyanoborohydride; other compounds of formula (I) wherein Z represents an optionally substituted heteroaryl group may be prepared similarly. A compound of formula (I) wherein -E-Z is hydrogen may be converted into the corresponding compound wherein E represents a C_{1-4} straight or branched alkylene chain by reaction with a compound of formula Hal-E-Z (wherein Hal represents a halogen atom, e.g. chloro or bromo), typically in the presence of a base such as sodium carbonate. A compound of formula (I) wherein -E-Z is hydrogen may be converted into the corresponding compound wherein -E-Z represents $-CONR^cR^d$ by reaction with a compound of formula Hal-$CONR^cR^d$ (wherein Hal is as defined above), typically in the presence of a base such as triethylamine. A compound of formula (I) wherein -E-Z is hydrogen may be converted into the corresponding compound wherein -E-Z represents $-CONR^cR^d$ or $-CONR^cOR^b$ by treatment with the appropriate compound of formula HNR^cR^d or R^bO-NHR^c in the presence of a carbonylating agent such as triphosgene or bis(4-nitrophenyl)carbonate, typically in the presence of a base such as triethylamine or diisopropylethylamine. A compound of formula (I) wherein -E-Z is hydrogen may be converted into the corresponding compound wherein -E-Z represents $-COR^a$ by treatment with the appropriate compound of formula R^aCO_2H and a condensing agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, typically in the presence of 1-hydroxybenzotriazole hydrate and 1-methyl-2-pyrrolidinone. A compound of formula (I)

wherein -E-Z is hydrogen may be converted into the corresponding compound wherein -E-Z represents $-SO_2NHCO_2C(CH_3)_3$ by treatment with *N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide. A compound of formula (I) wherein Z contains a carboxy group $-CO_2H$ may be obtained from the corresponding compound wherein Z contains a C_{2-6} alkoxycarbonyl moiety by saponification, which typically involves treatment with an inorganic base such as lithium hydroxide. A compound of formula (I) wherein R^1 is chloro may be converted into the corresponding compound wherein R^1 is hydrogen by treatment with hydrogen in the presence of a hydrogenation catalyst such as palladium on carbon. A compound of formula (ID) wherein R^3 represents $-SO_2R^e$ may be converted into the corresponding compound wherein R^3 is hydrogen by treatment with a base such as potassium hydroxide, typically in methanol. A compound of formula (ID) wherein R^3 is hydrogen may be converted into the corresponding compound wherein R^3 represents $-CH_2CONR^cR^d$ by reaction with a compound of formula Hal-$CH_2CONR^cR^d$ (wherein Hal is as defined above), typically in the presence of a base such as sodium carbonate.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a

particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode. Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potently inhibit the activity of human JNK1 and/or JNK2 and/or JNK3.

The JNK *in-vitro* enzyme assay determines the effect of test compounds on phosphorylation of the substrate, GST-c-Jun(1-89), at the Ser73 site using a heterogeneous time-resolved fluorometric assay method, DELFIA® (dissociation enhanced lanthanide fluorescence immunoassay). Glutathione plates are pre-coated with 100 µl/well GST-c-Jun (1 µg/ml) overnight at 4°C. After washing pre-coated plates 3 times with DELFIA® wash buffer (from Perkin-Elmer), 70 µl kinase assay buffer is added to all wells [20mM MOPS, pH 7.2, containing 25 mM β-glycerolphosphate, 5 mM $MgCl_2$, 5 mM EGTA and 1 mM DTT]. Test compounds dissolved in 20% DMSO/kinase assay buffer are added at 10 µl/well, giving a final concentration range of 0.3 nm to 10 µM. Recombinant human JNK is added in 10 µl kinase assay buffer, and the kinase reaction is initiated by the addition of ATP in 10 µl kinase assay buffer. After incubation for 60 minutes at room temperature, assay plates are washed 3 times with DELFIA® wash buffer (from Perkin-Elmer), to terminate the reaction and to remove assay components. Detection of phosphorylated substrate protein is initiated with the addition of 100 µl/well primary antibody [rabbit polyclonal anti-phospho Ser73 antibody used at 1/1000 dilution (from Cell Signalling Technology)]. After incubation for 60 minutes at room

temperature, plates are washed again and incubated for 30 minutes with a secondary anti-rabbit antibody labelled with europium (from Perkin-Elmer). A final wash step is carried out and DELFIA® enhancement solution (from Perkin-Elmer) is added. The fluorescent signal is read on a Tecan Ultra fluorescence plate reader (340 nm excitation/612 nM emission).

When tested in the above assay, the compounds of the accompanying Examples were all found to possess IC_{50} values for inhibition of human JNK1 and/or JNK2 and/or JNK3 enzyme activity of 5 μM or better.

EXAMPLES

The following LCMS conditions were used to obtain the retention times (RT) as described herein:

LCMS conditions

HP1100 (Diode Array) linked to a Finnigan LC-Q Mass Spectrometer, ESI mode with Pos/Neg ionisation.

Column:	Luna C18(2) 100 × 4.6 mm, 5 μm particle size Analytical column
Column temp:	35°C
Mobile phase:	A: Water + 0.08% formic acid B: Acetonitrile + 0.08% formic acid
Flow rate:	3 ml/min
Gradient:	Time (min) / % Composition B 0 / 5 4.40 / 95 5.30 / 95 5.32 / 5 6.50 / 5
Run time:	6.5 min
Typical injection volume:	10 μl
Detector wavelength:	DAD 200-400 nm

LCMS conditions

Waters 2690 linked to a Micromass ZMD Mass Spectrometer, ESI mode with Pos/Neg ionisation.

Column:	Luna C18(2) 100 × 4.6 mm, 5 µm particle size Analytical column
Column temp:	35°C
Mobile phase:	A: Water + 0.08% formic acid B: Acetonitrile + 0.08% formic acid
Flow rate:	3 ml/min

Gradient:

Time (min)	% Composition B
0	5
0.10	5
4.40	95
5.30	95
5.32	5
6.50	5

Run time:	6.5 min
Typical injection volume:	10 µl
Detector wavelength:	DAD 200-400 nm

LCMS conditions (pH 5.8)

HP1100 (Diode Array) linked to a Finnigan LC-Q Mass Spectrometer, ESI mode with Pos/Neg ionisation.

Column:	Luna C18(2) 100 × 4.6 mm, 5 µm particle size Analytical column
Column temp:	35°C
Mobile phase:	A: 5mM NH_4OAc pH 5.8 B: 95 : 5, MeCN : 100mM NH_4OAc pH 5.8
Flow rate:	3 ml/min

Gradient:

Time (min)	% Composition B
0	5
4.40	95
5.30	95
5.32	5

	6.50	5
Run time:	6.5 min	
Typical injection volume:	10 µl	
Detector wavelength:	DAD 200-400 nm	

The following preparative LC conditions were used to purify compounds as described herein:

Preparative LC conditions (Method A)

Gilson 215 liquid handler setup.

Column:	Luna C18(2) 250 × 21.2 mm, 5 µm particle size prep column
Column temp:	Ambient
Mobile phase:	A: Water + 0.08% formic acid B: Acetonitrile + 0.08% formic acid
Flow rate:	25 ml/min
Gradient:	Variable - depends on retention time of sample in LC-MS analysis
Run time:	20 min
Typical injection volume:	0.5-4.0 ml at 25 mg/ml
Detector wavelength:	210 and 254 nm

Preparative LC conditions (Method B)

Gilson 215 liquid handler setup.

Column:	Luna C18(2) 250 × 21.2 mm, 5 µm particle size prep column
Column temp:	Ambient
Mobile phase:	A: 10 mM NH_4OAc in water B: 10 mM NH_4OAc in acetonitrile
Flow rate:	25 ml/min
Gradient:	Variable - depends on retention time of sample in LC-MS analysis
Run time:	20 min
Typical injection volume:	0.5-4.0 ml at 25 mg/ml
Detector wavelength:	210 and 254 nm

Preparative LC conditions (Method C):

Gilson 215 liquid handler setup.

Column:	Luna C18(2) 100 × 21.2 mm, 5µm particle size prep column
Column temp:	Ambient
Mobile phase:	A: Water + 0.08% formic acid B: MeCN + 0.08 % formic acid
Flow rate:	20 ml/min
Gradient:	Variable- depends on retention of sample in LCMS screen
Run time:	10 mins
Typical injection volume:	0.5 ml at 25 mg/ml
Detector wavelength:	210 and 254 nm

The following chiral LC conditions were used to separate and analyse pairs of enantiomers in conjunction with the solvent systems and operating conditions as described herein:

Analytical chiral column conditions:

HP1050 HPLC System

Column:	Chiralpak® AD 250 × 4.6 mm, 10µm particle size analytical column
Column temp:	Ambient
Typical injection volume:	10 µl
Detector wavelength:	248 nm

Preparative chiral column conditions:

Varian Gradient HPLC system consisting of Varian 9012/9050/9100 Modules and Waters fraction collector.

Column:	Chiralpak® AD 250 × 20 mm, 10µm particle size prep column
Column temp:	Ambient
Typical injection volume:	1 ml
Detector wavelength:	248 nm

Abbreviations used

BOC - *tert*-Butoxycarbonyl
n-BuLi - *n*-Butyllithium
CDI - 1,1'-Carbonyldiimidazole
m-CPBA - *meta*-Chloroperbenzoic acid
DCM - Dichloromethane
DIPEA - Diisopropylethylamine
DMF - *N,N*-Dimethylformamide
DMSO - Dimethyl sulphoxide
d_6-DMSO - Dimethyl-d_6 sulphoxide
Et_2O - Diethyl ether
EtOAc - Ethyl acetate
EtOH - Ethanol
HOBt - 1-Hydroxybenzotriazole hydrate
IPA – Isopropanol
MeCN - Acetonitrile
MeOH - Methanol
d_4-MeOH - Methanol-d_4
NaOEt - Sodium ethoxide
NaOMe - Sodium methoxide
NMP - *N*-Methylpyrrolidinone
TEA - Triethylamine
TFA - Trifluoroacetic acid
THF - Tetrahydrofuran
DAPCy - Bis(dicyclohexylamino)palladium acetate
DMF-DEA - *N,N*-Dimethylformamide diethyl acetal
DMF-DMA - *N,N*-Dimethylformamide dimethyl acetal
EDC.HCl - 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU - *O*-(7-Azabenzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBTU - *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexaflurophosphate
r.t. – room temperature

INTERMEDIATE 1

{1-[(4-Methylphenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}boronic acid

To a solution of 3-iodo-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (CAS 664982-01-8) (2.0 g) in anhydrous THF (40 ml) at -78°C under nitrogen was added *n*-BuLi (2.5M in hexane, 3.0 ml). The mixture was stirred for 30 min at -78°C and triisopropyl borate (1.75 ml) was added. The mixture was stirred at -78°C for 1 hour, quenched with 2N HCl (10 ml) and allowed to warm to room temperature. The pH of the mixture was adjusted to pH 6-7 with 1N NaOH solution, saturated with NaCl and extracted with EtOAc (2 x 100 ml). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Trituration of the residue in Et_2O yielded the title compound as a yellow solid (350 mg, 22%). LCMS 317.1 $[M+H]^+$, RT 2.97 min. ^1H NMR 300 MHz (d_6-DMSO) 8.40 (1H, s), 8.35-8.30 (1H, m), 8.25 (1H, d), 8.00 (2H, d), 7.45 (2H, d), 7.25 (1H, q), 2.35 (3H, s).

INTERMEDIATE 2

3-(2,5-Dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1*H*-indole

To a solution of 2,4,5-trichloropyrimidine (1.25 g) in dry MeCN/water (20 ml/10 ml) under nitrogen was added 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (2.0 g) and Na_2CO_3 (1.4 g). The mixture was degassed 3 times before the addition of tetrakis(triphenylphosphine)palladium(0) (390 mg) took place. After degassing a further 3 times, the mixture was heated at reflux for 90 min. The resulting precipitate was filtered off and washed with water and Et_2O to afford the title compound as a white solid (2.48 g, 91%). ^{1}H NMR 300 MHz (d_6-DMSO) 9.00 (1H, s), 8.80 (1H, s), 8.55 (1H, d), 8.15 (2H, d), 8.05-8.02 (1H, s), 7.75 (1H, t), 7.64 (2H, t), 7.52-7.41 (2H, m).

INTERMEDIATE 3

3-(2,5-Dichloropyrimidin-4-yl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine

Prepared in a similar manner to Intermediate 2 from 2,4,5-trichloropyrimidine (500 mg) and Intermediate 1 (1167 mg) to afford the title compound as a solid (82 mg, 7%). LCMS 419 $[M+H]^+$, RT 4.58 min. ^{1}H NMR 300 MHz ($CDCl_3$) 9.00 (1H, s), 8.85 (1H, d), 8.65 (1H, s), 8.55 (1H, d), 8.15 (2H, d), 7.40-7.20 (3H, m), 2.40 (3H, s).

INTERMEDIATE 4

3-(2-Chloro-5-methylpyrimidin-4-yl)-1-(phenylsulfonyl)-1*H*-indole

Prepared in a similar manner to Intermediate 2 from 2,4-dichloro-5-methylpyrimidine (CAS 1780-31-0) (0.54 g) and 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (1.00 g). Purification by column chromatography on silica eluting with 0-40% EtOAc/heptane yielded the title compound as a white solid (602 mg, 47%). LCMS 384.1 $[M+H]^+$, RT 4.30 min. ^{1}H NMR 300 MHz ($CDCl_3$) 8.50 (1H, s), 8.30 (1H, d), 8.10-8.00 (2H, m), 7.90 (2H, d), 7.60 (1H, t), 7.50-7.30 (4H, m), 2.50 (3H, s).

INTERMEDIATE 5

6-Fluoro-1*H*-indole-3-carboxylic acid

To a solution of 6-fluoroindole (5.27 g) in dry THF (40 ml) under nitrogen cooled to 0°C was added pyridine (4.1 ml) followed by a solution of trichloroacetyl chloride (5.6 ml) in dry THF (20 ml). The mixture was allowed to warm to room temperature and stirred for 5 hours. More pyridine (4.1 ml) and trichloroacetyl chloride (5.6 ml) were added and the mixture stirred at room temperature for 72 hours. The mixture was concentrated *in vacuo* to a slurry and partitioned between EtOAc (100 ml), 2M HCl (75 ml) and water (175 ml). The aqueous phase was re-extracted with EtOAc (100 ml) and

the organic layers were combined, washed with saturated Na_2CO_3 solution (100 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting brown solid was dissolved in 1,4-dioxane (50 ml) and to this solution was added aqueous 2M NaOH solution (50 ml). The mixture was heated at 80°C for 30 min. After cooling, the mixture was partitioned between brine (100 ml) and DCM (250 ml), and the aqueous layer was washed with DCM (2 x 75 ml). The aqueous layer was acidified using 2M HCl and extracted with EtOAc (200 ml) and EtOAc/THF (100 ml/50 ml). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was triturated in Et_2O to give the title compound as a mustard yellow solid (5.53 g, 79%). LCMS No mass ion, RT 2.44 min. ^{1}H NMR 300 MHz (d_6-DMSO) 12.05 (1H, s, br), 11.85 (1H, s, br), 8.02-7.95 (1H, m), 7.28-7.23 (1H, m), 7.06-6.99 (1H, m).

INTERMEDIATE 6

3-(6-Fluoro-1*H*-indol-3-yl)-3-oxopropionitrile

To a solution of Intermediate 5 (5.5 g) in dry THF (50 ml) under nitrogen cooled to 0°C was added a solution of CDI in THF (25 ml). The mixture was stirred at room temperature for 1 hour. Meanwhile to a solution of *n*-BuLi (2.5M in hexanes) (55 ml) in dry THF (150 ml) under nitrogen cooled to -60°C was added dropwise MeCN (7.2 ml). The mixture was stirred at -60°C for 30 min. To this solution was added dropwise the previously prepared solution of indole intermediate. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. Saturated aqueous NH_4Cl solution (50 ml) was added and the THF removed *in vacuo*. The residue was diluted with EtOAc (200 ml) and the mixture filtered. The filtrate was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a brown solid (7.7 g, quantitative). ^{1}H NMR 300 MHz (d_6-DMSO) 12.25 (1H, s, br), 8.41 (1H, d), 8.17-8.11 (1H, m), 7.37-7.31 (1H, m), 7.18-7.09 (1H, m), 4.53 (2H, s).

INTERMEDIATE 7

(2*E*)-3-(Dimethylamino)-2-[(6-fluoro-1*H*-indol-3-yl)carbonyl]acrylonitrile

To a suspension of Intermediate 6 (7.7 g) in dry THF (150 ml) under nitrogen cooled to -20°C was added DMF-DEA (25 ml). The mixture was allowed to warm to room temperature and stirred for 3 hours. The THF was removed *in vacuo* and the residue partitioned between water (200 ml) and EtOAc (200 ml). The mixture was filtered and the solid obtained was triturated with Et_2O to give the title compound. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in*

vacuo. The resulting residue was triturated in Et_2O to give the title compound. This was combined with the earlier-isolated batch affording the title compound as a mustard yellow solid (5.84 g, 74%). LCMS 258 $[M+H]^+$, RT 2.66 min. ^1H NMR 300 MHz (d_6-DMSO) 11.75 (1H, s, br), 8.28 (1H, s), 8.10-8.05 (1H, m), 7.99 (1H, s), 7.23-7.19 (1H, m), 6.97-6.92 (1H, m), 3.33 (3H, s), 3.27 (3H, s).

INTERMEDIATE 8

4-(6-Fluoro-1*H*-indol-3-yl)-2-(methylthio)pyrimidine-5-carbonitrile

To a solution of Intermediate 7 (5.8 g) in EtOH (60 ml) under nitrogen was added NaOEt (3.68 g) and 2-methyl-2-thiopseudourea sulphate (3.76 g). The mixture was heated at reflux overnight. The resulting solid was filtered off, washed with water, washed with Et_2O and dried *in vacuo* to afford the title compound as a beige solid (3.81 g, 59%). LCMS 285 $[M+H]^+$, RT 4.01 min. ^1H NMR 300 MHz (d_6-DMSO) 12.15 (1H, s, br), 8.93 (1H, s), 8.62 (1H, s), 8.50-8.43 (1H, m), 7.40-7.31 (1H, m), 7.16-7.04 (1H, m), 2.68 (3H, s).

INTERMEDIATE 9

4-(1*H*-Indol-3-yl)-2-(methylthio)pyrimidine-5-carbonitrile

Prepared in a similar manner to Intermediate 8 from (2*E*)-3-(dimethylamino)-2-[(1*H*-indol-3-yl)carbonyl]acrylonitrile (CAS 314268-25-2) (3.1 g) and 2-methyl-2-thiopseudourea sulphate (3.87 g) using NaOH (60 mg) to give the title compound as a white solid (4.25 g, quantitative). LCMS 267 $[M+H]^+$, RT 3.80 min. ^1H NMR 400 MHz (d_6-DMSO) 8.94 (1H, s), 8.62 (1H, s), 8.49-8.46 (1H, m), 7.59-7.55 (1H, m), 7.31-7.24 (1H, m), 2.68 (3H, s).

INTERMEDIATE 10

4-(6-Fluoro-1*H*-indol-3-yl)-2-(methylsulfonyl)pyrimidine-5-carbonitrile

To a suspension of Intermediate 8 in DCM/THF (35 ml/35 ml) under nitrogen was added *m*-CPBA (70%) (4.9 g). The mixture was stirred at room temperature overnight. The resulting precipitate was filtered off and washed with Et_2O to afford the title compound as a yellow solid (1.43 g, 68%). LCMS 317 $[M+H]^+$, RT 3.04 min. ^1H NMR 300 MHz (d_6-DMSO) 12.50 (1H, s, br), 9.38 (1H, s), 8.80 (1H, s), 8.63-8.57 (1H, m), 7.46-7.41 (1H, m), 7.25-7.18 (1H, m), 3.52 (3H, s).

INTERMEDIATE 11

3-[2-(Methylsulfonyl)pyrimidin-4-yl]imidazo[1,2-*a*]pyridine

Prepared in a similar manner to Intermediate 10 from 3-[2-(methylsulfanyl)-pyrimidin-4-yl]imidazo[1,2-*a*]pyridine (CAS 328062-29-9) (420 mg) to afford the title compound as a lemon yellow solid (352 mg, 74%). LCMS 275 $[M+H]^+$, RT 1.55 min. ^1H NMR 300 MHz (d_6-DMSO) 9.88 (1H, d), 8.96 (1H, d), 8.90 (1H, s), 8.32 (1H, d), 7.87 (1H, d), 7.62 (1H, tr), 7.35 (1H, tr), 3.51 (3H, s).

INTERMEDIATE 12

2-(4-Aminopiperidin-1-yl)-*N,N*-dimethylacetamide bis(trifluoroacetate)

4-(BOC-amino)piperidine (300 mg) was partitioned between DCM (75 ml) and saturated aqueous Na_2CO_3 solution (75 ml). The aqueous layer was separated and extracted with DCM (50 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting white powder was dissolved in dry DMF (25 ml) under nitrogen and to this mixture was added Na_2CO_3 (318 mg) and 2-chloro-*N,N*-dimethylacetamide (0.31 ml). The reaction mixture was stirred at room temperature for 24 hours. Water (80 ml) was added and the mixture was extracted with DCM (2 x 100 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was suspended in dry DCM (20 ml) under nitrogen and to it was slowly added TFA. The mixture was stirred at room temperature for 5 hours. The solvent was removed *in vacuo* and the residue was triturated in Et_2O to afford the title compound as a white solid (476 mg, 77%). ^1H NMR 300 MHz (d_6-DMSO) 8.25-7.91 (4H, m, br), 7.79-7.69 (1H, m, br), 4.43-4.34 (1H, m), 3.91-3.78 (2H, m), 3.65-3.42 (2H, m), 3.20-3.01 (2H, m), 2.19-2.00 (2H, m), 1.93-1.76 (2H, m).

INTERMEDIATE 13

2-(4-Aminopiperidin-1-yl)acetamide bis(trifluoroacetate)

Prepared in a similar manner to Intermediate 12 from 4-(BOC-amino)piperidine hydrochloride (300 mg) and 2-bromoacetamide (414 mg) to afford the title compound as a white solid (600 mg, quantitative). ^1H NMR 300 MHz (d_6-DMSO) 9.82-9.62 (1H, m, br), 8.35-8.13 (3H, m, br), 4.82-4.63 (1H, m), 4.29-4.16 (2H, m), 3.67-3.45 (2H, m), 3.15-2.80 (2H, m), 2.92 (3H, s), 2.88 (3H, s), 2.16-1.96 (2H, m), 1.96-1.78 (2H, m).

INTERMEDIATE 14

2-(4-Aminopiperidin-1-yl)-*N*-methylacetamide bis(trifluoroacetate)

Prepared in a similar manner to Intermediate 12 from 4-(BOC-amino)piperidine (300 mg) and 2-chloro-*N*-methylacetamide (177 mg) to afford the title compound as a white solid (480 mg). LCMS 172 $[M+H]^+$ (free base), RT 0.34 min. ^1H NMR 300 MHz

(d_6-DMSO) 10.10-9.70 (1H, s, br), 8.52-8.40 (1H, s, br), 8.25-8.03 (3H, s, br), 4.00-3.55 (3H, m, br), 3.49-3.33 (2H, m), 3.12-2.93 (2H, m), 2.60 (3H, d), 2.06-1.93 (2H, m), 1.87-1.69 (2H, m).

INTERMEDIATE 15

N-[2-(4-Aminopiperidin-1-yl)ethyl]acetamide

To a solution of benzyl 1-(2-aminoethyl)piperidin-4-ylcarbamate (CAS 182223-52-5) (350 mg) in DCM (10 ml) was added TEA (0.34 ml) and acetyl chloride (0.09 ml). The reaction mixture was stirred at room temperature for 2 hours. Saturated aqueous $NaHCO_3$ (20 ml) was added and the mixture extracted with DCM (3 x 30 ml). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give a cream solid. This was dissolved in MeOH (10 ml) and to the solution was added palladium on carbon (10 mg) (10% palladium). The mixture was stirred under an atmosphere of nitrogen for 2 hours. The mixture was filtered through celite, washed with MeOH and the solution concentrated *in vacuo* to afford the title compound as a yellow oil (93 mg, 40%). ^{1}H NMR 300 MHz (d_6-DMSO) 3.33 (2H, t), 2.98-2.90 (2H, m), 2.70-2.60 (1H, m), 2.48 (2H, t), 2.14-2.05 (2H, m), 1.95 (3H, s), 1.88-1.80 (2H, m), 1.50-1.38 (2H, m).

INTERMEDIATE 16

1-(2,5-Dichloropyrimidin-4-yl)-1*H*-benzimidazole

Benzimidazole (100 mg) and THF (5 ml) were combined at room temperature under a nitrogen atmosphere. NaH (60% in oil) (41 mg) was added and effervescence observed. After 10 min, 2,4,5-trichloropyrimidine (155 mg) was added as a solution in THF (5 ml). After 30 min, the reaction was quenched by the addition of water (0.2 ml). The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica to give the title compound as a white solid (151 mg, 67%). LCMS 265/267 $[M+H]^+$, RT 3.17 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.20 (1H, s), 8.85 (1H, s), 7.95-7.75 (2H, m), 7.50-7.35 (2H, m).

INTERMEDIATE 17

1-(Propylsulfonyl)piperidin-4-amine trifluoroacetate

4-(BOC-amino)piperidine (300 mg) was added portionwise over 15 min to a solution of propanesulfonyl chloride (0.2 ml) and pyridine (0.145 ml) in DCM (10 ml) cooled to 0°C. The reaction mixture was stirred at room temperature for 2.5 days. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (100 ml) and

water (30 ml). The organic phase was washed with water (30 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. To a solution of the residue in DCM (15 ml) was added TFA (3 ml) and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo*, the residue was evaporated from toluene and then triturated with Et_2O to yield the title compound as a yellow powder (185 mg, 39%). LCMS 207 $[M+H]^+$ (free base), RT 0.93 min. ^1H NMR 300 MHz (d_6-DMSO) 7.96 (3H, s, br), 3.69-3.58 (2H, m), 3.25-3.09 (1H, m), 3.05-2.98 (2H, m), 2.95-2.81 (2H, m), 2.01-1.90 (2H, m), 1.75-1.61 (2H, m), 1.60-1.42 (2H, m), 0.98 (3H, t).

INTERMEDIATE 18

3-(2-Chloropyrimidin-4-yl)-1-(phenylsulfonyl)-1*H*-indole

Prepared in a similar manner to Intermediate 2 from 2,4-dichloropyrimidine (0.6 g) and 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (0.97 g). The title compound was obtained as an off-white solid (1.0 g, 68%). LCMS 370 $[M+H]^+$, RT 4.47 min. ^1H NMR 400 MHz ($CDCl_3$) 8.60 (1H, d), 8.40 (1H, d), 8.35 (1H, s), 8.03 (1H, d), 7.97 (2H, d), 7.62-7.57 (2H, m), 7.50 (2H, t), 7.45-7.47 (2H, m).

INTERMEDIATE 19

3-(2-Chloro-5-fluoropyrimidin-4-yl)-1-(phenylsulfonyl)-1*H*-indole

To a solution of DAPCy (CAS 628339-96-8) (6 mg) in EtOH (3 ml) was added 2,4-dichloro-5-fluoropyrimidine (CAS 2927-71-1) (92 mg), 1-(phenylsulfonyl)-1*H*-indol-3-ylboronic acid (200 mg) and potassium phosphate (236 mg). The mixture was stirred at room temperature overnight. Water (3 ml) was added and the precipitate was filtered off, washed with water and with Et_2O to afford the title compound as a pale yellow powder (82 mg, 38%). Tlc $R_f = 0.7$ (50% EtOAc/heptane). ^1H NMR 300 MHz ($CDCl_3$) 8.67 (1H, d), 8.52-8.47 (1H, m), 8.03 (1H, d), 7.95 (2H, d), 7.60 (1H, t), 7.55-7.40 (4H, m).

INTERMEDIATE 20

5-Chloro-4-(imidazo[1,2-*a*]pyridin-3-yl)pyrimidin-2(1*H*)-one

To a solution/suspension of 4-(imidazo[1,2-*a*]pyridin-3-yl)pyrimidin-2-amine (CAS 328062-37-9) (0.5 g) in dry DCM (50 ml) under nitrogen was added *N*-chlorosuccinimide (0.35 g). The reaction mixture was stirred at room temperature overnight and then heated at reflux for 24 hours. Water (30 ml) was added and the mixture extracted with DCM (150 ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica eluting with 5% MeOH/DCM to afford a yellow solid (140

mg). Analysis showed this to be the desired compound contaminated with succinimide. This was dissolved in acetic acid (5 ml) at 60°C and to this added a solution of sodium nitrite (84 mg) in water (2 ml). The mixture was heated at 60°C for 3 hours. After cooling to room temperature the mixture was basified to pH10 with 48% NaOH solution and diluted with water (10 ml). The resulting solid was filtered off, washed with water and dried *in vacuo* to give the title compound, contaminated with sodium acetate, as a sand-coloured solid (213 mg). LCMS 247/249 $[M+H]^+$, RT 1.24 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.92 (1H, d), 8.36 (1H, s), 8.01 (1H, s), 7.68 (1H, d), 7.49 (1H, dd), 7.04 (1H, dd).

INTERMEDIATES 21 AND 22

5-Chloro-1-(2-chloropyrimidin-4-yl)-1*H*-benzimidazole and 6-Chloro-1-(2-chloropyrimidin-4-yl)-1*H*-benzimidazole

5-Chlorobenzimidazole (2.04 g), 2,4-dichloropyrimidine (2 g), potassium carbonate (2.07 g) and DMF (20 ml) were combined and stirred at room temperature for 16 hours. The reaction mixture was diluted with EtOAc (100 ml), washed with water (2 x 30 ml), concentrated *in vacuo* and purified by column chromatography on silica eluting with 75-100% EtOAc/heptane to give:

5-Chloro-1-(2-chloropyrimidin-4-yl)-1*H*-benzimidazole (Intermediate 21) as a white solid (501 mg, 14%). Tlc R_f = 0.45 (EtOAc). LCMS 265/267 $[M+H]^+$, RT 3.50 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.30 (1H, s), 8.90 (1H, d), 8.45 (1H, d), 8.20 (1H, d), 7.90 (1H, d), 7.55 (1H, dd).

6-Chloro-1-(2-chloropyrimidin-4-yl)-1*H*-benzimidazole (Intermediate 22) as a white solid (426 mg, 12%). Tlc R_f = 0.40 (EtOAc). LCMS 265/267 $[M+H]^+$, RT 3.46 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.25 (1H, s), 8.95 (1H, d), 8.45 (1H, d), 8.20 (1H, d), 7.85 (1H, d), 7.45 (1H, dd).

INTERMEDIATE 23

3-[5-Chloro-2-(methylthio)pyrimidin-4-yl][1,2,4]triazolo[4,3-*a*]pyridine

5-Chloro-2-(methylthio)pyrimidine-4-carbonyl chloride (CAS 79686-02-5) (1.1 g) and DCM (25 ml) were combined at room temperature under a nitrogen atmosphere. 2-Hydrazinopyridine (534 mg) and TEA (1.4 ml) were added and stirring was continued for 16 hours. The solvents were removed *in vacuo* and the residue triturated with water and Et_2O to give a beige solid (1 g). This solid was then combined with $POCl_3$ (20 ml) under a nitrogen atmosphere and heated to 90°C for 3 days. The excess $POCl_3$ was removed *in*

vacuo and the residue triturated with water to give a tan solid which was further purified by column chromatography on silica eluting with 30% EtOAc/heptane to give the title compound as an off-white solid (105 mg, 8%). Tlc R_f = 0.63 (50% EtOAc/heptane). LCMS 278/280 $[M+H]^+$, RT 2.75 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.25 (1H, d), 9.00 (1H, s), 8.05 (1H, d), 7.70-7.60 (1H, m), 7.30-7.25 (1H, m), 2.65 (3H, s).

INTERMEDIATE 24

2-(4-Aminopiperidin-1-yl)-*N*-methylacetamide bis(hydrochloride)

4-(BOC-amino)piperidine hydrochloride (1.06 g) was partitioned between DCM (75 ml) and saturated aqueous Na_2CO_3 solution (75 ml). The aqueous layer was separated and extracted with DCM (50 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting white powder was dissolved in dry DMF (20 ml) under nitrogen and to this mixture was added Na_2CO_3 (617 mg) and 2-chloro-*N*-methylacetamide (626 mg). The reaction mixture was stirred at room temperature for 24 hours. Water (80 ml) was added and the mixture was extracted with DCM (2 x 100 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was suspended in dry MeOH (10 ml) under nitrogen and to it was slowly added 2N HCl in Et_2O (10 ml). The mixture was stirred at room temperature for 5 hours. The solvent was removed *in vacuo* and the residue was triturated in Et_2O to afford the title compound as a white solid (1.2 g, 94%). LCMS 172 $[M+H]^+$ (free base), RT 0.29 min. ^{1}H NMR 300 MHz (d_6-DMSO) 10.30-10.10 (1H, m, br), 8.80-8.30 (4H, m, br), 4.00-3.70 (3H, m, br), 3.60-3.00 (4H, m), 2.55 (3H, s, br), 2.20-1.80 (4H, m).

INTERMEDIATE 25

3-(2,5-Dichloropyrimidin-4-yl)imidazo[1,2-a]pyridine

Zinc bromide (3.45 g) was dried at 130°C under vacuum for 1 hour and then allowed to cool to room temperature. A solution of 3-bromoimidazolepyridine (2 g) in THF (40 ml) was charged into a three neck round bottomed flask under nitrogen and cooled to –78°C. *n*-BuLi (2.5M in hexanes) (4.9ml) was added dropwise to the cooled solution, which was left to stir for 1 hour. A solution of the dried zinc bromide in THF (30ml) was added dropwise to the cooled mixture and stirred at –78°C. After 30 minutes the reaction mixture was allowed to warm to room temperature over 1 hour. 2,4,5-trichloropyrimidine (1.86g) and tetrakis(triphenylphosphine)palladium(0) (587mg) were added to the mixture, which was heated to 70°C overnight. The reaction mixture was

concentrated *in vacuo* and purified by column chromatography on reverse phase silica eluting with 40%-100% (MeOH + 0.04% formic acid)/(H_2O + 0.04% formic acid) to afford the title compound as a beige solid (803 mg, 30%). LCMS 265/267 $[M+H]^+$ RT 2.63 min. ^1H NMR 300 MHz (d_6-DMSO) 9.60 (1H, d), 8.95 (1H, s), 8.85 (1H, s), 7.85 (1H, d), 7.70-7.60 (1H, m), 7.35-7.25 (1H, m).

INTERMEDIATE 26

1-(Isopropylsulfonyl)piperidin-4-amine hydrochloride

To a solution of 4-(BOC-amino)piperidine (500 mg) in dry DCM under nitrogen cooled to 0°C (5 ml) was added DIPEA (0.435 ml) followed by isopropylsulfonyl chloride (0.279 ml). The reaction mixture was allowed to warm to r.t. and stirred overnight and diluted with DCM (50 ml). The organic layer was washed with aqueous 1M HCl solution (15 ml), washed with saturated aqueous Na_2CO_3 solution (15 ml), washed with saturated brine (15 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting white solid (629 mg) was dissolved in MeOH (1 ml) and cooled to 0°C. A solution of HCl (2M in Et_2O) (10 ml) was added to the reaction mixture, which was allowed to warm to room temperature and stirred overnight. The resulting precipitate was filtered off, washed with Et_2O and dried *in vacuo* to afford the title compound as a pale yellow solid (474 mg, 78%). ^1H NMR 300 MHz ($CDCl_3$ + Na_2CO_3 in D_2O) 4.70 (1H, s, br, partially exchanging), 3.83-3.74 (2H, m), 3.18 (1H, hep), 3.00-2.90 (2H, m), 2.85-2.75 (1H, m), 1.92-1.82 (2H, m), 1.47-1.34 (2H, m), 1.34 (6H, 2Xd).

INTERMEDIATE 27

1-[(1-Methyl-1*H*-imidazol-4-yl)sulfonyl]piperidin-4-amine bis(hydrochloride)

Prepared in a similar manner to Intermediate 26 from 4-(BOC-amino)piperidine (500 mg) and 1-methylimidazole-4-sulphonyl chloride (496 mg) to afford the title compound as a yellow solid (849 mg, quantitative). ^1H NMR 300 MHz ($CDCl_3$ + Na_2CO_3 in D_2O) 7.50 (1H, s), 7.42 (1H, s), 4.70 (2H, s, br), 3.82-3.72 (2H, m), 3.75 (3H, s), 2.78-2.65 (2H, m), 1.90-1.80 (2H, m), 1.52-1.36 (2H, m).

INTERMEDIATE 28

1-(Pyridin-2-ylmethyl)piperidin-4-amine tris(hydrochloride)

To a solution of 4-(BOC-amino)piperidine (500 mg) in DCE (6 ml) under nitrogen was added 2-pyridinecarboxaldehyde (0.24 ml) and DIPEA (0.44 ml) followed by sodium triacetoxyborohydride (635 mg). The reaction mixture was stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue dissolved in DCM (100 ml). The organic

layer was washed with sodium hydrogencarbonate solution (25 ml), washed with brine (25 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. This was dissolved in dry MeOH (5 ml) and to this mixture added a solution of HCl (2M in Et_2O) (12 ml). The reaction was stirred at room temperature overnight. The resulting precipitate was filtered off, washed with Et_2O and dried *in vacuo* to yield the title compound as a green solid (744 mg, quantitative). LCMS (pH 5.8) 192 $[M+H]^+$ (Free base) RT 1.12 min. ^1H NMR 300 MHz ($CDCl_3$ + Na_2CO_3 in D_2O) 8.55 (1H, d), 7.56 (1H, t), 7.40 (1H, d), 7.15 (1H, t), 4.90 (1.5H, s, br, partially exchanging), 3.65 (2H, s), 2.90-2.80 (2H, s), 2.72-2.61 (1H, m), 2.20-2.05 (2H, m), 1.85-1.75 (2H, m), 1.50-1.35 (2H, m).

INTERMEDIATE 29

1-(Pyridin-4-ylmethyl)piperidin-4-amine tris(hydrochloride)

Prepared in a similar manner to Intermediate 28 from 4-(BOC-amino)piperidine (500 mg) and 4-pyridinecarboxaldehyde (0.24 ml) to afford the title compound as a yellow solid (715 mg, 95%) LCMS (pH 5.8) 192 $[M+H]^+$ (Free base) RT 1.10 min. ^1H NMR 300 MHz ($CDCl_3$ + Na_2CO_3 in D_2O) 8.55 (2H, d), 7.25 (2H, d), 4.90 (0.5H, m, br, partially exchanging), 3.50 (2H, s), 2.85-2.75 (2H, s), 2.72-2.61 (1H, m), 2.12-2.00 (2H, m), 1.85-1.75 (2H, m), 1.50-1.32 (2H, m).

INTERMEDIATE 30

3-Iodo-1-(phenylsulfonyl)-1*H*-indole-7-carbonitrile

To a solution of 7-cyanoindole (CAS 96631-87-7) (410 mg) in DCM (25ml) cooled to 0°C was added *N*-iodosuccinimide (780 mg) portionwise. The reaction mixture was stirred with slow warming to r.t.. After 2 hours the reaction mixture was diluted with water (50 ml) and extracted into DCM (3 x 100 ml). The combined organic fractions were dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give 7-cyano-3-iodoindole as a brown solid. A portion of this solid (70 mg) was dissolved in dry THF (5ml) under nitrogen and cooled to 0°C for the addition of NaH (60% dispersion in mineral oil) (16mg) to take place. After warming to room temperature and stirring for 30 min, the solution was cooled to 0°C and benzenesulfonylchloride (0.05ml) was added dropwise. The reaction mixture was allowed to warm to RT and stirred for 2 hours. The solvents were removed *in vacuo*. Purification by column chromatography on silica eluting with 0-50% EtOAc/heptane afforded the title compound as an off-white solid (50mg, 39%). LCMS RT 4.17 min. ^1H NMR 300 MHz ($CDCl_3$) 8.10 (2H, d), 8.00 (1H, s), 7.75-7.50 (5H, m), 7.40-7.35 (1H, m).

INTERMEDIATE 31

3-(2,5-Dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1*H*-indole-7-carbonitrile

Prepared in a similar manner to Intermediate 25 from Intermediate 30 (600mg). Purification by column chromatography on silica eluting with 0-100% EtOAc/Heptane afforded the title compound as an off-white solid (148mg, 24%). LCMS RT 4.37 min. ^{1}H NMR 300 MHz ($CDCl_3$) 9.05 (1H, s), 8.85 (1H, d), 8.70 (1H, s), 8.10 (2H, d), 7.75 (1H, d), 7.70-7.65 (1H, m), 7.60-7.55 (2H, m), 7.50-7.45 (1H, t), 1.50-1.32 (2H, m).

INTERMEDIATE 32

3-Iodo-1-(phenylsulfonyl)-1*H*-indole-6-carbonitrile

To a solution of 6-cyanoindole (1.0 g) in dry DMF (20 ml) under nitrogen was added KOH (785 mg) followed by iodine portionwise over 10 min. The reaction mixture was stirred at r.t. for 30 min. The reaction was diluted with water (70 ml) resulting in a precipitate. This was filtered off, washed with water, washed with sodium thiosulphate solution and dried *in vacuo* to give 6-cyano-3-iodo-indole as a solid. This was dissolved in THF (25ml), cooled to 0°C and NaH (60% dispersion in mineral oil) (350mg) added. After 10 minutes stirring benzenesulfonylchloride (0.90ml) was added. The reaction mixture was stirred at r.t. for 5 minutes. Water (50ml) was added to the reaction mixture and the precipitate formed was collected by filtration and dried *in vacuo* to afford the title compound as a yellow solid (2.59g, 95%). LCMS 406/407 $[M-H]^+$, RT 4.29 min. ^{1}H NMR 300 MHz (d_6-DMSO) 8.45 (2H, s), 8.20 (2H, d), 7.80-7.75 (2H, m), 7.65-7.60 (2H, m), 7.55 (1H, d).

INTERMEDIATE 33

3-Hydroxy-1-imidazo[1,2-a]pyridin-3-yl-3-methoxy-2-methylpropan-1-one

To a solution of imidazo[1,2-a]pyridine (5.0 g) in dry DCM (80 ml) under nitrogen cooled to 0°C was added portionwise $AlCl_3$ (11.3 g) over 30 min. The reaction mixture was allowed to warm to r.t. and stirred for 75 min before being heated at reflux for propionic anhydride (3.8 ml) to be added dropwise over 15 mins. Heating at reflux continued for a further 2 hours. After cooling to r.t. the mixture was concentrated *in vacuo* and to the residue added ice/water (100 ml). The mixture was made basic by the addition of 2M NaOH solution and the aqueous solution was extracted with EtOAc (2 x 300 ml). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed in vacuo. The resulting brown semi-solid was triturated in Et_2O/hexane and the resulting solid was filtered off and dried *in vacuo*. A solution/suspension of this product

in DMF-DMA was heated at reflux for 120 hours. The reaction mixture was allowed to cool to r.t. and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 5-10% MeOH/DCM afforded the title compound (1:1 mixture of diastereomers) as a tallow solid (0.64 g, 8%). TLC R_f 0.33 (10% MeOH/DCM). LCMS 235 $[M+H]^+$, RT 1.53 and 1.61 min. ^{1}H NMR 300 MHz ($CDCl_3$) 9.66 (1H, d), 8.40 (1H, s), 7.70 (1H, d), 7.55 (1H, t), 7.12 (1H, t), 4.80 (1H, d), 4.69 (1H, dd), 3.56 (1H, dq), 3.42 (3H, s), 1.42 (3H, d).

INTERMEDIATE 34

3-Iodo-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[3,2-c]pyridine

To a mixture of 6-azaindole (CAS 271-341) (1.72 g) and KOH (2.4 g) in dry DMF (50 ml) under nitrogen was added iodine (3.73 g) portionwise over 15 min. The mixture was stirred at r.t. for a further 90 min and poured into water (600 ml) containing sodium metabisulfite solution (100 ml). Adjusting the solution to pH10 caused the product to precipitate out. The solid was extracted with EtOAc (500 ml). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a yellow solid (2.98 g). This solid was dissolved in dry THF (50 ml) and to the mixture was added portionwise NaH (60% dispersion in mineral oil) (630 mg). The mixture was stirred for a further 15 min. *Para*-toluenesulfonyl chloride (2.42 g) was added in one portion and the mixture stirred at r.t. for 2 hours. The mixture was poured into water (600 ml) and extracted with EtOAc (400 ml). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 0-10% MeOH/DCM yielded the title compound as a solid (3.37 g, 58%). LCMS 399 $[M+H]^+$, RT 2.99 min. ^{1}H NMR 300 MHz ($CDCl_3$) 8.70 (1H, s), 8.55 (1H, d), 7.90-7.75 (3H, m), 7.70 (1H, s), 7.30 (2H, d), 2.40 (3H, s).

INTERMEDIATE 35

3-(2,5-Dichloropyrimidin-4-yl)-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[3,2-c]pyridine

Prepared in a similar manner to Intermediate 25 from Intermediate 34 (2.0 g) and 2,4,5-trichloropyrimidine (840 mg). Purification by column chromatography on silica eluting with 40-100% EtOAc/heptane yielded the title compound as a yellow solid (144 mg, 7%). LCMS 419/421 $[M+H]^+$, RT 3.25 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.55 (1H, s), 9.05 (1H, s), 8.85 (1H, s), 8.60 (1H, d), 8.10 (2H, d), 8.05 (1H, d), 7.45 (2H, d), 2.35 (3H, s).

EXAMPLE 1

Formic acid - Ethyl 4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate (1:1)

To a solution/suspension of Intermediate 2 (100 mg) in MeOH (20 ml) was added KOH (21 mg). The mixture was stirred at room temperature for 60 min and then heated at reflux for 30 min. The mixture was concentrated *in vacuo* and the residue triturated in water. The solid was filtered off, washed with water, washed with Et_2O and dried *in vacuo*. This was dissolved in DMF (4 ml) under nitrogen and to it added ethyl 4-amino-1-piperidinecarboxylate (0.26 ml) and Na_2CO_3 (160 mg). The mixture was heated at 120°C for 6 hours. The DMF was removed *in vacuo* and the residue partitioned between EtOAc and water (75 ml/25 ml). The organic layer was washed with brine (25 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by prep HPLC (Method A) afforded the title compound as a yellow solid (4 mg, 4%). LCMS 400/402 $[M+H]^+$ (free base), RT 3.55 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.60 (1H, s, br), 8.49 (1H, s), 8.30 (1H, s), 8.26 (1H, s) 7.48 (1H, d), 7.28 (1H, d), 7.25-7.14 (2H, m), 4.11-3.90 (5H, m), 3.11-2.82 (2H, m), 2.05-1.86 (2H, m), 1.51-1.34 (2H, m), 1.18 (3H, s).

EXAMPLE 2

tert-Butyl 4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

To a solution/suspension of Intermediate 2 (500 mg) in dry DMF (20 ml) under nitrogen was added 1-BOC-4-aminopiperidine hydrochloride (1.5 g) and Na_2CO_3 (1.3 g). The mixture was heated at 120° C for 2 hours. The mixture was concentrated *in vacuo* and the residue dissolved in MeOH (40 ml). To this was added KOH (100 mg) and the mixture stirred at room temperature overnight. Water (30 ml) was added and the MeOH removed *in vacuo*. The residue was extracted with EtOAc (150 ml) and washed with brine (30 ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 40% EtOAc/heptane afforded the title compound as a white solid (290 mg, 55%). TLC R_f 0.29 (40% EtOAc/heptane). LCMS 428/430 $[M+H]^+$, RT 4.06 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.60 (1H, s, br), 8.49 (1H, s), 8.27 (1H, s), 7.50 (1H, d), 7.30-7.14 (3H, m), 4.06-3.90 (3H, m), 3.00-2.77 (2H, m), 2.02-1.83 (2H, m), 1.50-1.32 (2H, m), 1.40 (9H, s).

EXAMPLE 3

tert-Butyl 3-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}azetidine-1-carboxylate

Prepared in a similar manner to Example 2 from Intermediate 2(100 mg) and 3-aminoazetidine-1-carboxylic acid *tert*-butyl ester (51 mg). Purification by trituration with Et_2O gave the title compound as a yellow solid (5.2 mg, 5%). LCMS 344/346 $[M\text{-}t\text{Bu}]^+$, RT 3.84 min. ^1H NMR 300 MHz (d_4-MeOH) 8.60 (1H, d, br), 8.45 (1H, s), 8.22 (1H, s), 7.50-7.45 (1H, m), 7.25-7.15 (2H, m), 4.82-4.72 (1H, m), 4.37-4.30 (2H, m), 3.96-3.88 (2H, m), 1.50 (9H, s).

EXAMPLE 4

tert-Butyl 3-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}pyrrolidine-1-carboxylate

Prepared in a similar manner to Example 2 from Intermediate 2 (100 mg) and (+/-)-3-amino-1-*N*-BOC-pyrrolidine (55 mg). Purification by prep HPLC (Method B) gave the title compound as a yellow solid (3 mg, 3%). LCMS 358/360 $[M+H]^+$, RT 4.09 min. ^1H NMR 300 MHz (d_6-DMSO) 8.60 (1H, s, br), 8.47 (1H, s), 8.30 (1H, s), 7.62-7.53 (1H, m), 7.48 (1H, d), 7.25-7.10 (2H, m), 4.48-4.32 (1H, m), 3.67-3.40 (2H, m), 3.30-3.20 (2H, m), 2.22-2.10 (1H, m), 2.00-1.85 (1H, m) 1.42, 1.38 (9H, 2 x s).

EXAMPLE 5

4-{[5-Chloro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

Prepared in a similar manner to Example 2 from Intermediate 3 (82.4 mg) and the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (204 mg). Purification by prep HPLC (Method A) afforded the title compound as a white solid (5.9 mg, 7%). TLC R_f 0.12 (1% MeOH/DCM). LCMS 400.2 $[M+H]^+$, RT 2.47 min. ^1H NMR 300 MHz (d_6-DMSO) 12.45 (1H, s), 8.95 (1H, d, br), 8.60 (1H, s), 8.35 (1H, d), 8.30 (1H, s), 7.40 (1H, d), 7.25 (1H, s, br), 6.50 (1H, t), 4.10-3.80 (3H, m), 3.05 (2H, quin), 2.90-2.70 (2H, m), 1.90 (2H, s), 1.40 (2H, q), 1.00 (3H, t).

EXAMPLE 6

N-Ethyl-4-({5-methyl-4-[1-(phenylsulfonyl)-1*H*-indol-3-yl]pyrimidin-2-yl}amino)-piperidine-1-carboxamide

To a solution/suspension of Intermediate 4 (277 mg) in dry DMF (5 ml) under nitrogen was added 1-BOC-4-aminopiperidine hydrochloride (855 mg) and Na_2CO_3 (765 mg). The mixture was heated at 120°C overnight. After cooling to room temperature, the mixture was taken up in EtOAc (200 ml) and washed with water (3 x 100 ml) and saturated NaCl solution (100 ml). The organic layer was separated, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was partially purified by

column chromatography on silica eluting with 60% EtOAc/heptane. The resulting solid was dissolved in dry THF (10 ml) and to this was added 2N HCl (5 ml). The solution was stirred at room temperature for 24 hours. The pH of the mixture was adjusted to pH7 with 2N NaOH and extracted with DCM (4 x 75 ml). The organic layers were combined, washed with saturated NaCl solution (100 ml), separated, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was partially purified by column chromatography on silica eluting with 80% EtOAc/heptane. The resulting solid (65 mg) was dissolved in DCE (2 ml) and to it was added TEA (20 µl) followed by ethyl isocyanate (11 µl). The mixture was stirred for 2 hours at room temperature, adsorbed onto silica and purified by column chromatography eluting with 5% MeOH/DCM to afford the title product as a white solid (41 mg, 11%). LCMS 519 $[M+H]^+$, RT 3.31 min. ^1H NMR 300 MHz ($CDCl_3$) 8.25 (1H, s), 8.15 (1H, d), 8.05 (1H, d), 8.00-7.85 (3H, m), 7.55 (1H, d), 7.45 (2H, t), 7.40 (1H, t), 7.30 (1H, t), 5.00 (1H, d), 4.40 (1H, t), 4.15-4.00 (1H, m), 3.95 (2H, d), 3.25 (2H, dt), 3.00 (2H, t), 2.35 (3H, s), 2.10 (2H, d), 1.45 (2H, dq), 1.15 (3H, t).

EXAMPLE 7

N-Ethyl-4-{[4-(1*H*-indol-3-yl)-5-methylpyrimidin-2-yl]amino}piperidine-1-carboxamide

To a solution of Example 6 (36 mg) in MeOH (20 ml) was added NaOH (90 mg). The mixture was stirred at room temperature for 63 hours. The solvent was removed *in vacuo* and the residue taken up in water (75 ml) and extracted with DCM (3 x 75 ml). The organic layers were combined, dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography on silica eluting with 6% MeOH/DCM to afford the title compound as a pale yellow solid (21 mg, 81%). TLC R_f 0.2 (5% MeOH/DCM). LCMS 379 $[M+H]^+$, RT 1.83 min. ^1H NMR 300 MHz ($CDCl_3$) 8.60 (1H, s), 8.45 (1H, d), 8.15 (1H, s), 7.70 (1H, d), 7.45 (1H, d), 7.35-7.20 (2H, m), 4.95 (1H, d), 4.40 (1H, t), 4.20-4.00 (1H, m), 3.95 (2H, d), 3.30 (2H, quin), 3.05 (2H, dt), 2.35 (3H, s), 2.15 (2H, d), 1.50 (2H, dq), 1.15 (3H, t).

EXAMPLE 8

Ethyl 4-{[5-cyano-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

To a solution of Intermediate 9 (4.25 g) in $CHCl_3$ (300 ml) was added *m*-CPBA (70%) (11.8 g). The mixture was stirred at room temperature overnight. The resulting solid was filtered off, washed with $CHCl_3$ (2 x 200 ml) and dried *in vacuo* to give a 1:1 mixture of the corresponding sulphoxide and sulphone as a yellow solid (4.25 g). A

portion of this solid (100 mg) and ethyl 4-amino-1-piperidinecarboxylate (130 mg) were heated at reflux in ethoxyethanol for 15 min. The mixture was allowed to cool, and the resulting suspension diluted with water (20 ml), EtOAc (20 ml) and THF (5 ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 30-70% EtOAc in 40-60 petrol containing 10% THF, followed by trituration with Et_2O, gave the title compound as an off-white solid (55 mg, 37%). TLC R_f 0.2 (50% EtOAc/heptane). LCMS 391 $[M+H]^+$, RT 3.66 min. ^1H NMR 400 MHz (d_6-DMSO, 130°C) 8.56 (1H, s), 8.54 (1H, s), 8.46 (1H, s), 7.53-7.46 (2H, m,), 7.26-7.17 (2H, m), 4.24-4.13 (1H, m), 4.12-4.06 (2H, q), 4.05-3.96 (2H, m), 3.09-3.00 (2H, m), 2.05-1.96 (2H, m), 1.64-1.53 (2H, m), 1.26-1.22 (3H, t).

EXAMPLE 9

tert-Butyl 4-{[5-cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

Intermediate 10 (1.43 g), 1-BOC-4-aminopiperidine (1.60 g) and TEA (3.0 ml) were heated at reflux in EtOH (70 ml) for 30 min. The reaction mixture was allowed to cool to room temperature and the white precipitate was collected by filtration. The product was washed with EtOH, water and Et_2O. Purification by column chromatography on silica eluting with 5-10% MeOH/DCM furnished the title compound as a yellow powder (1.03 g, 52%). TLC R_f 0.37 (5% MeOH/DCM). ^1H NMR 300 MHz (d_6-DMSO) 12.03 (1H, d, br), 8.75-8.68 and 8.49-8.43 (1H, 2 x m), 8.67 and 8.60 (1H, 2 x s), 8.54-8.50 (1H, m), 8.23-8.13 (1H, m), 7.38-7.28 (1H, m), 7.19-7.09 and 7.07-6.98 (1H, 2 x m), 4.18-3.90 (3H, m), 3.08-2.74 (2H, m), 2.03-1.83 (2H, m), 1.54-1.38 (2H, m), 1.42 (9H, s).

EXAMPLE 10

2-(4-{[5-Cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*,*N*-dimethylacetamide

Prepared in a similar manner to Example 9 from Intermediate 10 (50 mg) and Intermediate 12 (98 mg), to yield the title compound as a yellow powder (17 mg, 25%). TLC R_f 0.39 (15% MeOH/DCM). LCMS 422 $[M+H]^+$, RT 1.85 min. ^1H NMR 400 MHz (d_6-DMSO, 130°C) 11.63 (1H, s, br), 8.59-8.53 (1H, m), 8.55 (1H, s), 8.48 (1H, s), 7.51 (1H, d, br), 7.29 (1H, dd), 7.02 (1H, dt), 4.05-3.93 (1H, m), 3.22 (2H, s), 3.01-2.89 (8H, m), 2.92-2.30 (2H, m), 2.02-1.93 (2H, m), 1.78-1.66 (2H, m).

EXAMPLE 11

2-(4-{[5-Cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-acetamide

Prepared in a similar manner to Example 9 from Intermediate 10 (50 mg) and Intermediate 13 (92 mg) to yield the title compound as a beige powder (20 mg, 32%). TLC R_f 0.39 (15% MeOH/DCM). LCMS 394 $[M+H]^+$, RT 1.74 min. ^{1}H NMR 400 MHz (d_6-DMSO, 130°C) 8.60-8.53 (1H, m), 8.55 (1H, s), 8.47 (1H, s), 7.51 (1H, d, br), 7.29 (1H, dd), 7.02 (1H, dt), 6.85-6.52 (2H, s, br), 4.05-3.93 (1H, m), 3.00-2.88 (4H, m), 2.41-2.30 (2H, m), 2.04-1.93 (2H, m), 1.81-1.69 (2H, m).

EXAMPLE 12

2-(4-{[5-Cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

Prepared in a similar manner to Example 9 from Intermediate 10 (850 mg) and Intermediate 14 (150 mg) to yield the title compound as a white powder (43 mg, 42%). LCMS 408 $[M+H]^+$, RT 1.83 min. ^{1}H NMR 300 MHz (d_6-DMSO) 12.02 (1H, d), 8.78-8.70 and 8.53-8.45 (1H, 2 x m), 8.65 and 8.60 (1H, 2 x s), 8.52 and 8.49 (1H, 2 x s), 8.28-8.19 (1H, m), 7.75-7.62 (1H, m), 7.40-7.28 (1H, m), 7.11-6.99 (1H, m), 3.97-3.74 (1H, m), 3.00-2.80 (4H, m), 2.64 (3H, d), 2.30-2.09 (2H, m), 2.01-1.83 (2H, m), 1.76-1.59 (2H, m).

EXAMPLE 13

Formic acid - *N*-[2-(4-{[5-cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}-piperidin-1-yl)ethyl]acetamide (1:1)

Prepared in a similar manner to Example 9 from Intermediate 10 (66.5 mg) and Intermediate 15 (46.5 mg). Purification by prep HPLC (Method A) afforded the title compound as a white solid (32 mg, 36%). LCMS 422 $[M+H]^+$ (free base), RT 1.78 min. ^{1}H NMR 400 MHz (d_6-DMSO, 130°C) 8.58-8.55 (1H, m), 8.52 (1H, s), 8.47 (1H, s), 8.20 (1H, s), 7.49 (1H, d, br), 7.29 (1H, dd), 7.16 (1H, s, br), 7.01 (1H, dt), 4.03-3.90 (1H, m), 3.22-3.17 (2H, m), 2.95-2.89 (2H, m), 2.50-2.45 (2H, m), 2.25-2.19 (2H, m), 2.00-1.91 (2H, m), 1.82 (3H, m), 1.74-1.64 (2H, m).

EXAMPLE 14

N-Ethyl-4-{[4-(imidazo[1,2-*a*]pyridin-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxamide

Prepared in a similar manner to Example 9 from Intermediate 11 (100 mg) and the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (112

mg). Purification by column chromatography on silica eluting with 0-10% MeOH/DCM afforded the title compound as a brown glass (21 mg, 16%). LCMS 366 $[M+H]^+$, RT 1.51 min. ^{1}H NMR 400 MHz (d_6-DMSO) 8.58 (1H, s), 8.27 (1H, d), 7.75 (1H, d), 7.47 (1H, t), 7.34 (1H, d), 7.22-7.10 (1H, m), 6.50 (1H, t), 4.03-3.87 (3H, m), 3.09-2.97 (2H, m), 2.88-2.74 (2H, m), 1.98-1.72 (2H, m), 1.45-1.27 (2H, m), 0.98 (3H, t).

EXAMPLE 15

2-(4-{[4-(Imidazo[1,2-*a*]pyridin-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

Prepared in a similar manner to Example 9 from Intermediate 11 (100 mg) and Intermediate 14 (215 mg). Purification by prep HPLC (Method B) afforded the title compound as a cream solid (8.4 mg, 6.3%). LCMS (pH 5.8) 366 $[M+H]^+$, RT 2.37 min. ^{1}H NMR 300 MHz (d_6-DMSO) 10.27-10.11 (1H, m), 8.53 (1H, s), 8.26 (1H, d), 7.76 (1H, d), 7.70-7.63 (1H, m), 7.45 (1H, t), 7.34 (1H, d), 7.17-7.10 (2H, m), 3.80-3.66 (1H, m), 2.90 (2H, s), 2.87-2.77 (2H, m), 2.63 (3H, d), 2.30-2.11 (2H, m), 2.04-1.85 (2H, m), 1.70-1.50 (2H, m).

EXAMPLE 16

tert-Butyl 4-{[4-(1*H*-benzimidazol-1-yl)-5-chloropyrimidin-2-yl]amino}piperidine-1-carboxylate

Intermediate 16 (150 mg), 1-BOC-4-aminopiperidine.HCl (134 mg), DMF (5 ml) and TEA (0.087 ml) were combined and heated to 60°C for 72 hours. The reaction mixture was diluted with EtOAc (20 ml) and washed with water (2 x 20 ml). The organic layer was separated, concentrated *in vacuo* onto silica and purified by column chromatography to give the title compound as a white solid (115 mg, 50%). LCMS 373/375 $[M-t\text{Bu}]^+$, RT 3.90 min. ^{1}H NMR 300 MHz (d_6-DMSO) 8.75 (1H, s, br), 8.65 (1H, s, br), 8.00-7.85 (1H, m), 7.85-7.70 (2H, m), 7.45-7.30 (2H, m), 4.05-3.75 (3H, m), 2.95-2.7 (2H, m), 1.95-1.80 (2H, m), 1.50-1.30 (2H, m), 1.40 (9H, s).

EXAMPLE 17

4-{[4-(1*H*-Benzimidazol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

Prepared in a similar manner to Example 16 from 1-(2-chloropyrimidin-4-yl)-1*H*-benzimidazole (CAS 710328-94-2) (112 mg) and the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (101 mg). Purification by prep HPLC (Method A) afforded the title compound as a white solid (65 mg, 37%). LCMS 366 $[M+H]^+$, RT 2.27 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.10 (1H, s, br), 8.75-8.65 (0.5H,

m), 8.50-8.35 (0.5H, m), 8.40 (1H, d), 7.80-7.40 (4H, m), 7.15 (1H, d), 6.50 (1H, t), 4.10-3.90 (3H, m), 3.15-3.00 (2H, m), 2.95-2.70 (2H, m), 2.00-1.80 (2H, m), 1.50-1.30 (2H, m), 1.00 (3H, t).

EXAMPLE 18

2-(4-{[4-(1*H*-Benzimidazol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)acetamide

Prepared in a similar manner to Example 16 from 1-(2-chloropyrimidin-4-yl)-1*H*-benzimidazole (71 mg) and Intermediate 13 (119 mg). Purification by prep HPLC (Method B) afforded the title compound as a white solid (30 mg, 32%). LCMS (pH 5.8) 352 $[M+H]^+$, RT 1.38 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.10 (1H, s), 8.80-8.65 (0.5H, m), 8.50-8.35 (0.5H, m), 8.40 (1H, d), 7.80-7.30 (4H, m), 7.25-7.10 (3H, m), 3.90-3.70 (1H, m), 3.00-2.80 (4H, m), 2.30-2.10 (2H, m), 2.05-1.85 (2H, m), 1.70-1.50 (2H, m).

EXAMPLE 19

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(pyrrolidin-3-yl)pyrimidin-2-ylamine hydrochloride

Example 4 (183 mg) was stirred as a suspension in a solution of HCl (2M in Et_2O) (5 ml) at room temperature for 95 min. The reaction mixture was concentrated *in vacuo* to give the title compound as a yellow solid (150 mg, quantitative). LCMS 314/316 $[M+H]^+$ (free base), RT 1.74 min. ^{1}H NMR 400 MHz (d_6-DMSO) 12.00 (1H, s, br), 9.40-9.10 (1H, m), 8.65-8.52 (1H, m), 8.51 (1H, s), 8.34 (1H, s), 7.74-7.65 (1H, m), 7.50 (1H, d), 7.25-7.14 (2H, m), 4.62-4.50 (1H, m), 3.50-3.15 (4H, m), 2.31-2.15 (1H, m), 2.13-2.00 (1H, m).

EXAMPLE 20

4-(6-Fluoro-1*H*-indol-3-yl)-2-(piperidin-4-ylamino)pyrimidine-5-carbonitrile

A solution of Example 9 (1.0 g) in DCM (40 ml) and TFA (10 ml) was stirred at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue partitioned between DCM (100 ml) and 2N HCl (300 ml). The aqueous phase was separated, basified with 3M aqueous NaOH and extracted with DCM (4 x 200 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as an off-white solid (0.44 g, 57%). LCMS 337 $[M+H]^+$, RT 1.78 min. ^{1}H NMR 300 MHz (d_6-DMSO) 12.00 (1H, d, br), 8.78-8.70 and 8.55-8.45 (1H, 2 x m), 8.65 and 8.59 (1H, 2 x s), 8.51 and 8.48 (1H, 2 x s), 8.23-8.15 (1H, m), 7.39-7.28 (1H, m), 7.12-6.98 (1H, m), 4.06-3.82 (1H, m), 3.09-2.92 (2H, m), 2.66-2.50 (2H, m), 1.97-1.78 (2H, m), 1.53-1.35 (2H, m).

EXAMPLE 21

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

To a suspension/solution of Example 2 (290 mg) in MeOH/DCM (10 ml/10 ml) was added a solution of HCl (2.0M in Et_2O, 6.8 ml) and the mixture stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue dissolved in dry DCM (40 ml) under nitrogen. To this was added TEA (0.48 ml) followed by ethyl isocyanate (0.05 ml) dropwise. The mixture was stirred at room temperature for 2 hours. Water (30 ml) was added and the mixture extracted with DCM (100 ml). The organic layer was washed with water (20 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 1% MeOH/EtOAc afforded the title compound as a white solid (151 mg, 56%). TLC R_f 0.18 (EtOAc). LCMS 398/401 $[M+H]^+$, RT 2.81 min. ^1H NMR 300 MHz (d_6-DMSO) 11.90-11.80 (1H, s, br), 8.75-8.50 (1H, s, br), 8.48 (1H, s), 8.27 (1H, s), 7.50 (1H, d), 7.30-7.14 (3H, m), 6.00 (1H, t), 4.07-3.88 (3H, m), 3.09-3.00 (2H, m), 2.89-2.70 (2H, m), 2.02-1.80 (2H, m), 1.47-1.32 (2H, m), 0.98 (3H, t).

EXAMPLE 22

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylazetidine-1-carboxamide

Prepared in a similar manner to Example 21 from Example 3 (50 mg). Purification by prep HPLC (Method B) gave the title compound as an off-white solid (5 mg, 11%). LCMS (pH 5.8) 371/373 $[M+H]^+$, RT 2.93 min. ^1H NMR (70°C) 400 MHz (d_6-DMSO) 11.70-11.60 (1H, s, br), 8.58 (1H, d), 8.40 (1H, s), 8.27 (1H, s), 7.16 (1H, d), 7.50 (1H, d), 7.23-7.15 (2H, m), 6.08-6.01 (1H, m), 4.68-4.59 (1H, m), 4.18-4.10 (2H, t), 3.82-3.75 (2H, m), 3.10-3.00 (2H, m), 1.05-0.96 (3H, t).

EXAMPLE 23

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpyrrolidine-1-carboxamide

Example 19 (65 mg) was dissolved in DCM (5 ml) and stirred under nitrogen at room temperature. TEA (0.1 ml) and ethyl isocyanate (0.02 ml) were added to the reaction mixture. After 30 min a solid had formed, which was collected by filtration. The solid was washed with DCM and E_2O, and dried *in vacuo* overnight to afford the title compound as a pink solid (30 mg, 42%). LCMS 385/387 $[M+H]^+$, RT 2.79 min. ^1H NMR 300 MHz (d_6-DMSO) 11.90-11.80 (1H, s, br), 8.70-8.50 (1H, m), 8.45 (1H, s), 8.30 (1H, s), 7.60-7.45 (2H, m), 7.25-7.10 (2H, m), 6.15-6.05 (1H, m), 4.55-4.35 (1H, m), 3.60-3.20 (4H, m), 3.10-3.00 (2H, m), 3.20-2.05 (1H, m), 2.00-1.90 (1H, m), 1.05-0.90 (3H, t).

EXAMPLE 24

4-{[5-Cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

Prepared in a similar manner to Example 23 from Example 20 (30 mg) and ethyl isocyanate (8 µl) in THF (5 ml). Purification by column chromatography on silica eluting with 0-5% MeOH/DCM afforded the title compound as a white powder (24 mg, 67%). LCMS 408 $[M+H]^+$, RT 2.95 min. ^{1}H NMR 400 MHz (d_6-DMSO, 110°C) 8.60-8.51 (2H, m), 8.48 (1H, s), 7.70 (1H, d), 7.29 (1H, dd), 7.03 (1H, dt), 6.13-6.05 (1H, m), 4.19-4.08 (1H, m), 4.03-3.94 (2H, m), 3.12 (2H, dq), 2.95-2.84 (2H, m), 2.00-1.90 (2H, m), 1.60-1.49 (2H, m), 1.07 (3H, t).

EXAMPLE 25

Ethyl *N*-[(4-{[5-cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]-beta-alaninate

Prepared in a similar manner to Example 23 from Example 20 (30 mg) and ethyl 3-isocyanato-propionate (13 µl) in THF (5 ml). Purification by column chromatography on silica eluting with 0-5% MeOH/DCM afforded the title compound as a white powder (31 mg, 72%). LCMS 480 $[M+H]^+$, RT 3.11 min. ^{1}H NMR 400 MHz (d_6-DMSO, 110°C) 11.70 (1H, s, br), 8.60-8.51 (2H, m), 8.48 (1H, s), 7.69 (1H, d), 7.29 (1H, dd), 7.02 (1H, dt), 6.25-6.19 (1H, m), 4.17-4.05 (3H, m), 4.00-3.89 (2H, m), 3.33 (2H, dt), 2.95-2.83 (2H, m), 2.51-2.46 (2H, m), 1.99-1.89 (2H, m), 1.58-1.48 (2H, m), 1.23 (3H, t).

EXAMPLE 26

Ethyl *N*-[(4-{[5-cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]glycinate

Prepared in a similar manner to Example 23 from 4 Example 20 (30 mg) and ethyl isocyanatoacetate (11 µl) in THF (5 ml). Purification by column chromatography on silica eluting with 0-5% MeOH/DCM afforded the title compound as a white powder (26 mg, 62%). LCMS 466 $[M+H]^+$, RT 3.02 min. ^{1}H NMR 400 MHz (d_6-DMSO, 110°C) 8.60-8.52 (2H, m), 8.48 (1H, s), 7.71 (1H, d), 7.29 (1H, dd), 7.03 (1H, dt), 6.61-6.53 (1H, m), 4.19-4.08 (3H, m), 4.03-3.95 (2H, m), 3.79 (2H, d), 3.00-2.92 (2H, m), 2.01-1.93 (2H, m), 1.62-1.50 (2H, m), 1.22 (3H, t).

EXAMPLE 27

4-{[5-Cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxamide

Trimethylsilyl isocyanate (0.18 ml) was added to a suspension of Example 20 (30 mg) in DCM (3 ml). The reaction mixture was stirred for 42 hours under nitrogen, diluted with DCM (60 ml) and washed with saturated aqueous $NaHCO_3$ solution (60 ml). The solid that formed at the interface was filtered off, washed with water and Et_2O, and dried *in vacuo* to furnish the title compound as a white powder (11 mg, 33%). LCMS 380 $[M+H]^+$, RT 2.59 min. ^1H NMR 300 MHz (d_6-DMSO) 12.00 (1H, s, br), 8.74-8.67 and 8.48-8.40 (1H, 2 x m), 8.63 and 8.55 (1H, 2 x s), 8.54 and 8.52 (1H, 2 x s), 8.19-8.08 (1H, m), 7.39-7.28 (1H, m), 7.13-6.95 (1H, m), 5.97 (2H, s, br), 4.18-3.88 (3H, m), 2.95-2.69 (2H, m), 2.00-1.77 (2H, m), 1.53-1.34 (2H, m).

EXAMPLE 28

4-(6-Fluoro-1*H*-indol-3-yl)-2-{[1-(1*H*-imidazol-2-ylmethyl)piperidin-4-yl]amino}-pyrimidine-5-carbonitrile

Sodium cyanoborohydride (38 mg) and imidazole-2-carboxaldehyde (35 mg) were added to a suspension of Example 20 (100 mg) in MeOH (20 ml) under nitrogen. The reaction mixture was stirred for 72 hours at room temperature, at which point a further portion of sodium cyanoborohydride (19 mg) was added and stirring was continued for a further 18 hours. Saturated K_2CO_3 solution (2 ml) was added and the solvent was removed *in vacuo*. The residue was partitioned between water (60 ml) and EtOAc (60 ml). The aqueous phase was extracted with DCM (50 ml) and more EtOAc (2 x 50 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow powder was purified by column chromatography on silica eluting with 0-10% MeOH/DCM to afford the title compound as a white powder (37 mg, 30%). TLC R_f 0.3 (15% MeOH/DCM). LCMS 417 $[M+H]^+$, RT 1.78 min. ^1H NMR 300 MHz (d_6-DMSO) 12.10-11.85 (2H, m), 8.75-8.69 and 8.50-8.43 (1H, 2 x m), 8.65 and 8.59 (1H, 2 x s), 8.53 and 8.50 (1H, 2 x d), 8.23-8.17 (1H, m), 7.39-7.29 (1H, m), 7.08-7.00 (1H, m), 6.99-6.89 (2H, m), 3.97-3.75 (1H, m), 3.56 and 3.51 (2H, 2 x s), 2.93-2.81 (2H, m), 2.24-2.04 (2H, m), 2.01-1.83 (2H, m), 1.69-1.52 (2H, m).

EXAMPLE 29

N-[(4-{[5-Cyano-4-(6-fluoro-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]glycine

A solution of LiOH (2 mg) in water (0.5 ml) was added to a solution of Example 26 (13 mg) in THF (2 ml). The yellow solution was stirred for 16 hours at room temperature. The reaction was quenched by the addition of glacial acetic acid (10 drops),

and the solvents were removed *in vacuo*. Water (3 ml) was added and the mixture stirred vigorously. The white precipitate was filtered off and dried *in vacuo* to yield the title compound as an off-white powder (7 mg, 54%). LCMS 338 $[M+H]^+$, RT 2.62 min. ^1H NMR 300 MHz (d_6-DMSO, 130°C) 8.59-8.52 (2H, m), 8.48 (1H, s), 7.61 (1H, d), 7.29 (1H, dd), 7.04 (1H, dt), 4.21-4.10 (1H, m), 4.03-3.95 (2H, m), 3.73 (2H, s), 3.03-2.95 (2H, m), 2.04-1.93 (2H, m), 1.65-1.53 (2H, m).

EXAMPLE 30

4-(6-Fluoro-1*H*-indol-3-yl)-2-{[1-(propylsulfonyl)piperidin-4-yl]amino}pyrimidine-5-carbonitrile

Prepared in a similar manner to Example 9 using Example 20 (80 mg), 1-(propylsulfonyl)piperidin-4-amine trifluoroacetate (120 mg) and TEA (0.22 ml). Purification by column chromatography on silica eluting with 0-2% MeOH/DCM and further purification by prep HPLC (Method A) afforded the title compound as a white powder (6.9 mg, 6%). LCMS 443 $[M+H]^+$, RT 3.60 min. ^1H NMR 400 MHz (d_6-DMSO) 12.11-11.97 (1H, s, br), 8.75-8.41 (3H, m), 8.25 (1H, d), 7.40-7.29 (1H, m), 7.20-7.00 (1H, m), 4.13-3.95 (1H, m), 3.70-3.60 (2H, m), 3.11-2.90 (4H, m), 2.12-1.95 (2H, m), 1.78-1.52 (4H, m), 1.00 (3H, q).

EXAMPLE 31

4-(6-Fluoro-1*H*-indol-3-yl)-2-{[1-(1*H*-imidazol-4-ylmethyl)piperidin-4-yl]amino}pyrimidine-5-carbonitrile

Prepared in a similar manner to Example 28 from Example 20 (80 mg), 4(5)-imidazolecarboxaldehyde (28 mg) and sodium cyanoborohydride (30 mg). Purification by HPLC (Method A) afforded the title compound as a white powder (19 mg, 19%). LCMS 417 $[M+H]^+$, RT 1.57 min. ^1H NMR 300MHz (d_6-DMSO) 12.10-11.95 (1H, d, br), 8.75-8.44 (3H, m), 8.18 (1H, d), 7.55 (1H, s), 7.39-7.28 (1H, m), 7.08-7.00 (1H, m), 6.93-6.83 (1H, m), 3.98-3.73 (1H, m), 2.98-2.82 (2H, m), 2.14-1.82 (4H, m), 1.68-1.50 (2H, m).

EXAMPLE 32

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine .

Example 2 (3.67 g) was heated at reflux in a 10% TFA in DCM (100 ml) solution for 90 min. The reaction was allowed to cool to room temperature before diluting with DCM (100ml) and pouring into a saturated solution of $NaHCO_3$ (100 ml). The resulting precipitate was collected by filtration and washed with DCM before drying *in vacuo* to

yield the title compound as an off-white powder (2.79 g, 99%). LCMS 328 $[M+H]^+$, RT 1.71 min. ^{1}H NMR 300 MHz (d_6-DMSO) 8.62 (1H, s, br), 8.49 (1H, d), 8.29 (1H, s), 7.53-7.45 (2H, m), 7.26-7.14 (2H, m), 4.11-3.93 (1H, m), 3.50-3.35 (2H, m), 3.03-2.92 (2H, m), 2.16-2.02 (2H, m), 1.75-1.60 (2H, m).

EXAMPLE 33

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

Example 32 (70 mg) was dissolved in DMF (10 ml) before the addition of 2-chloro-*N*-methylacetamide (23 mg) and Na_2CO_3 (121 mg) took place. The reaction was heated at 80°C under nitrogen for 2 hours before being allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to afford the title compound as a brown solid (3.5 mg, 5%). LCMS 401/399 $[M+H]^+$, RT 1.79 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.63 (1H, d), 8.50 (1H, s), 8.18 (1H, s), 7.47 (1H, d), 7.28-7.17 (2H, m), 4.65 (1H, s, br), 4.04-3.89 (1H, m), 3.05 (2H, s), 2.98-2.90 (2H, m), 2.80 (3H, s), 2.43-2.33 (2H, m), 2.17-2.08 (2H, m), 1.81-1.66 (2H, m).

EXAMPLE 34

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-methoxypiperidine-1-carboxamide

Methoxylamine hydrochloride (10 mg) was dissolved in DCM (5 ml) and cooled to -78°C under nitrogen. TEA (0.05 ml) was added followed by triphosgene (13 mg) and the mixture was stirred at 0°C for 30 min. Example 32 (40 mg) and TEA (0.05 ml) were added and the mixture was stirred with warming to room temperature overnight. The reaction mixture was diluted with water (10 ml) and extracted with DCM (3 x 20 ml). The DCM fractions were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give a mixture of product and starting material. The mixture was purified by column chromatography on silica eluting with 0-100% EtOAc/heptane to give the title compound as a yellow solid (5.2 mg, 11%). LCMS 401/403 $[M+H]^+$, RT 2.64 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.75 (1H, s, br), 9.75 (1H, s), 8.60 (1H, s, br), 8.50 (1H, s), 8.25 (1H, s), 7.50 (1H, d), 7.30 (1H, d), 7.20-7.10 (2H, m), 4.00-3.80 (3H, m), 3.55 (3H, s), 2.80-2.75 (2H, m), 2.00-2.85 (2H, m), 1.50-1.35 (2H, m).

EXAMPLE 35

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N,N*-dimethylpiperidine-1-carboxamide

To a solution/suspension of Example 32 (50 mg) in DCM (5 ml) and THF (3 ml) at room temperature under nitrogen was added TEA (0.04 ml) and dimethylcarbamyl chloride (0.015 ml). The mixture was stirred overnight. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (100 ml) and water (25 ml). The organic layer was washed with brine (25 ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting solid was triturated with Et_2O to give the title compound as a white powder (51 mg, 84%). LCMS 399/401 $[M+H]^+$, RT 3.01 min. ^1H NMR 300 MHz (d_6-DMSO) 11.80 (1H, s, br), 8.55 (1H, s, br), 8.45 (1H, s), 8.20 (1H, s), 7.45 (1H, d), 7.25 (1H, d), 7.20-7.05 (2H, m), 4.00-3.85 (1H, m), 3.60-3.50 (2H, m), 2.85-2.75 (2H, m), 2.70 (6H, s), 2.00-1.85 (2H, m), 1.55-1.40 (2H, m).

EXAMPLE 36

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(morpholin-4-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

Prepared in a similar manner to Example 35 from Example 32 (50mg) and 4-morpholinylcarbamyl chloride (0.02 ml) to give the title compound as a yellow solid (15 mg, 22%). LCMS 441/443 $[M+H]^+$, RT 2.91 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.60 (1H, s, br), 8.45 (1H, d), 8.25 (1H, s), 7.45 (1H, d), 7.30 (1H, d), 7.20-7.10 (2H, m), 4.10-3.90 (1H, m), 3.70-3.60 (2H, m), 3.60-3.55 (4H, m), 3.20-3.10 (4H, m), 2.95-2.85 (2H, m), 2.10-1.85 (2H, m), 1.60-1.40 (2H, m).

EXAMPLE 37

N-(2-{4-[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-ylamino]piperidin-1-yl}-2-oxoethyl)-acetamide

To a solution of Example 32 (50 mg) in DCM (2 ml) was added *N*-acetylglycine (27 mg), followed by a solution of EDC.HCl (44 mg) in DCM (1 ml) and a solution of HOBt (catalytic amount) in NMP (1 ml). The reaction mixture was stirred overnight at room temperature, then diluted with DCM (50 ml) and washed with water (10 ml). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 10% MeOH/DCM afforded the title compound as an off-white powder (29 mg, 45%). LCMS 427 $[M+H]^+$, RT 2.46 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s), 8.72-8.54 (1H, m), 8.49 (1H, s), 8.29 (1H, s), 7.99 (1H, t), 7.49 (1H, d), 7.35 (1H, d), 7.26-7.15 (2H, m), 4.40-4.29 (1H, m), 4.11-3.81 (4H, m), 3.22-3.09 (1H, m), 2.90-2.70 (1H, m), 2.10-1.93 (2H, m), 1.88 (3H, s), 1.56-1.31 (2H, m).

EXAMPLES 38-53

Examples 38-53 were prepared using parallel synthesis techniques as described below. Example 32 (280 mg) was dissolved in NMP (3.8 ml). Portions of this solution (200 µl) were dispensed into the first 18 wells of a Whatman 48 deep well plate. Solutions of the appropriate carboxylic acid (0.5 M in NMP, 200 µl) were added to the individual wells. A solution of EDC.HCl (0.2 M in DCM, 500 µl) and a solution of HOBt (0.2 M in NMP) (50 µl) were added to each well and the plate shaken overnight. The solvents were removed *in vacuo* and DMSO (500 µl) added to each well. The desired products from each well were isolated by prep HPLC Method A) to yield on average 1 mg of the title compounds.

EXAMPLE 38

N-(1-acetylpiperidin-4-yl)-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 370/372 $[M+H]^+$, RT 2.75 min.

EXAMPLE 39

5-chloro-4-(1*H*-indol-3-yl)-*N*-[1-(methoxyacetyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 400/402 $[M+H]^+$, RT 2.80 min.

EXAMPLE 40

5-chloro-4-(1*H*-indol-3-yl)-*N*-[1-(tetrahydrofuran-3-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 426/428 $[M+H]^+$, RT 2.90 min.

EXAMPLE 41

5-chloro-4-(1*H*-indol-3-yl)-*N*-[1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 440/442 $[M+H]^+$, RT 2.90 min.

EXAMPLE 42

5-chloro-*N*-[1-(3-furoyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 422/424 $[M+H]^+$, RT 3.20 min.

EXAMPLE 43

5-chloro-4-(1*H*-indol-3-yl)-*N*-(1-isonicotinoylpiperidin-4-yl)pyrimidin-2-amine

LCMS 433/435 $[M+H]^+$, RT 2.55 min.

EXAMPLE 44

N-{4-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]phenyl}acetamide

LCMS 489/491 $[M+H]^+$, RT 2.90 min.

EXAMPLE 45

5-chloro-*N*-{1-[4-(dimethylamino)benzoyl]piperidin-4-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 475/477 $[M+H]^+$, RT 3.55 min.

EXAMPLE 46

4-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N'*,*N'*-dimethyl-4-oxobutanohydrazide

LCMS 470/472 $[M+H]^+$, RT 2.30 min.

EXAMPLE 47

5-chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(1-methyl-1*H*-pyrrol-2-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 435/437 $[M+H]^+$, RT 3.45 min.

EXAMPLE 48

5-[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]imidazolidine-2,4-dione

LCMS 468/470 $[M+H]^+$, RT 2.45 min.

EXAMPLE 49

N-{1-[(1-acetylpiperidin-4-yl)carbonyl]piperidin-4-yl}-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 481/483 $[M+H]^+$, RT 2.70 min.

EXAMPLE 50

(3-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-3-oxo-propyl)-urea

LCMS 442/444 $[M+H]^+$, RT 2.40 min.

EXAMPLE 51

5-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-2-one

LCMS 439/441 $[M+H]^+$, RT 2.50 min.

EXAMPLE 52

5-chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(5-methylpyrazin-2-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 448/450 $[M+H]^+$, RT 3.00 min.

EXAMPLE 53

5-chloro-4-(1H-indol-3-yl)-N-{1-[(3-methylisoxazol-5-yl)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 451/453 $[M+H]^+$, RT 3.10 min.

EXAMPLE 54

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-[3-(4-methylpiperazin-1-yl)propyl]piperidine-1-carboxamide

Prepared in a similar manner to Example 34 from Example 32 and 1-(3-aminopropyl)-4-methylpiperazine. The crude product was purified by prep HPLC (Method B) to give the title compound as a brown solid (19 mg, 24%). LCMS (pH 5.8) 511/513 $[M+H]^+$, RT 1.68 min. ^{1}H NMR 300 MHz (d_6-DMSO 70°C) 11.65 (1H, s, br), 8.60 (1H, d), 8.40 (1H, s), 8.20 (1H, s), 7.50 (1H, d), 7.25-7.10 (2H, m), 7.00-6.95 (1H, d), 6.40-6.35 (1H, m), 4.05-3.90 (3H, m), 3.15-3.05 (2H, m), 2.90-2.80 (2H, m), 2.40-2.35 (2H, m), 2.35-2.25 (2H, m), 2.15 (3H, s), 2.00-1.90 (2H, m), 1.60-1.50 (2H, m), 1.50-1.40 (2H, m).

EXAMPLE 55

Formic acid - 4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-[2-(dimethylamino)ethyl]piperidine-1-carboxamide (2:1)

To a solution of bis(4-nitrophenyl)carbonate (28 mg) and DIPEA (0.02 ml) in DMF (2 ml) stirring at room temperature was added Example 32 (30 mg). After 20 min *N,N*-dimethylethylenediamine (0.01 ml) was added and the mixture heated in a microwave at 130°C for 10 min. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to give the title compound as a yellow solid (6.4 mg, 16%). LCMS 442/444 $[M+H]^+$ (free base), RT 1.86 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.60 (1H, d), 8.45 (1H, s), 8.30 (2H, s), 8.15 (1H, s), 7.45 (1H, d), 7.25-7.10 (2H, m), 4.15-4.00 (3H, m), 3.50-3.45 (2H, m), 3.25-3.20 (2H, m), 3.10-2.95 (2H, m), 2.40 (6H, s), 2.15-2.05 (2H, m), 1.60-1.40 (2H, m).

EXAMPLE 56

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-methoxy-*N*-methylpiperidine-1-carboxamide

To a solution of bis(4-nitrophenyl)carbonate (84 mg) and DIPEA (0.05 ml) in DMF (3 ml) stirring at room temperature was added *N,O*-dimethylhydroxylamine hydrochloride (27 mg). After 1 hour, Example 32 (90 mg) was added and the mixture

heated in a microwave at 100°C for 10 min. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to give the title compound as a pale yellow solid (35 mg, 31%). LCMS 354/356 $[M+H]^+$, RT 3.16 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.60 (1H, s, br), 8.45 (1H, s), 8.25 (1H, s), 7.50 (1H, d), 7.30 (1H, d) 7.25-7.10 (2H, m), 4.10-3.90 (3H, m), 3.55 (3H, s), 3.10-2.95 (2H, m), 2.35(3H, s), 2.15-1.90 (2H, m), 1.55-1.40 (2H, m).

EXAMPLE 57

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylbutanamide

Prepared in a similar manner to Example 33 from Example 32 (248 mg) and 2-bromo-*N*-methylbutanamide (CAS 42275-49-0) (150 mg). The reaction was diluted with DCM (20 ml) and washed with water (10 ml). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was triturated with Et_2O to give the title compound as an off-white solid (59 mg, 20%). LCMS 427 $[M+H]^+$, RT 1.88 min. ^1H NMR 300 MHz ($CDCl_3$) 8.60 (2H, m), 8.40 (1H, s), 8.24 (1H, s), 7.46 (1H, d), 7.35-7.23 (2H, m), 6.97 (1H, s, br), 5.05 (1H, d), 4.07-3.95 (1H, m), 2.89-2.84 (6H, m), 2.58-2.47 (1H, m), 2.44-2.32 (1H, m), 2.28-2.13 (2H, m), 1.83-1.75 (2H, m), 0.99 (3H, t).

EXAMPLE 58

2-{4-[(5-Chloro-4-{1-[2-(methylamino)-2-oxoethyl]-1*H*-indol-3-yl}pyrimidin-2-yl)amino]piperidin-1-yl}-*N*-methylacetamide

Prepared in a similar manner to Example 33 from Example 32 (90 mg), 2-chloro-*N*-methylacetamide (65 mg) and Na_2CO_3 (64 mg). Purification by prep HPLC (Method B) afforded the title compound as a pale yellow solid (20 mg, 9%). LCMS (pH 5.8) 470 $[M+H]^+$, RT 1.67 min. ^1H NMR 300 MHz ($CDCl_3$) 8.58 (1H, d), 8.24 (2H, s), 7.39-7.29 (3H, m), 7.17 (1H, s, br), 5.36 (1H, d), 5.13 (1H, d), 4.89 (2H, s), 4.05-3.93 (1H, m), 3.06 (2H, s), 2.94-2.85 (5H, m), 2.73 (3H, d), 2.47-2.37 (2H, m), 2.24-2.13 (2H, m), 1.68-1.57 (2H, m).

EXAMPLE 59

Ethyl (3*R*,4*S*)-4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-3-methoxypiperidine-1-carboxylate

Prepared in a similar manner to Example 2 from Intermediate 2 (103 mg) and (3*R*, 4*S*)-4-amino-3-methoxypiperidine-1-carboxylic acid ethyl ester (62 mg). Purification by

column chromatography eluting with 20-50% EtOAc/heptane followed by trituration with Et_2O afforded the title compound as a white powder (35 mg). LCMS 430 $[M+H]^+$, RT 3.63 min. ^1H NMR 300MHz (d_6-DMSO) 11.87 (1H, s), 8.78-8.55 (1H, m), 8.49 (1H, s), 8.29 (1H, s), 7.50 (1H, d), 7.26-7.12 (1H, m), 7.05-6.78 (1H, m), 4.37-4.22 (1H, m), 4.20-3.93 (4H, m), 3.67-3.52 (1H, m), 3.30 (3H, s), 3.10-2.88 (2H, m), 1.90-1.60 (2H, m), 1.20 (3H, t).

EXAMPLE 60

tert-Butyl 4-{[4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

To a solution of Intermediate 18 (600 mg) in dry DMF (10 ml) under nitrogen was added DIPEA (0.84 ml) and 1-BOC-4-aminopiperidine hydrochloride (573 mg). The reaction mixture was heated at 90°C for 3 days. The solvent was removed *in vacuo* and the residue dissolved in MeOH (40 ml) and to this added KOH (136 mg). The mixture was heated at reflux overnight. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to afford the title compound as a cream solid (5 mg, 1%). LCMS 394 $[M+H]^+$, RT 2.43 min. ^1H NMR 300 MHz (d_6-DMSO) 11.70 (1H, s, br), 8.60-8.50 (1H, m), 8.22 (1H, s), 8.13 (1H, d), 7.45 (1H, d), 7.21-7.10 (2H, m), 7.03 (1H, d), 6.93 (1H, d), 4.08-3.90 (2H, m), 3.86-3.75 (1H, m), 3.00-2.75 (2H, m), 2.04-1.87 (2H, m), 1.75-1.65 (1H, m), 1.40 and 1.38 (9H, 2 x s), 1.28-1.20 (1H, m).

EXAMPLE 61

N-Ethyl-4-{[5-fluoro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxamide

Prepared in a similar manner to Example 2 from Intermediate 19 (80 mg) and the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (55 mg). Purification by prep HPLC (Method A followed by Method B) afforded the title compound as a white solid (0.8 mg, 1%). LCMS (pH 5.8) 383 $[M+H]^+$, RT 2.40 min. ^1H NMR 300 MHz (d_4-MeOH) 8.72 (1H, d), 8.58 (1H, s), 8.12 (1H, s), 8.08 (1H, d), 7.49 (1H, d), 7.28-7.18 (2H, m), 4.15-4.05 (3H, m), 3.25-3.20 (2H, m), 3.09-3.00 (2H, m), 2.22-2.08 (2H, m), 1.60-1.42 (2H, m), 1.13 (3H, t).

EXAMPLE 62

4-{[5-Chloro-4-(imidazo[1,2-*a*]pyridin-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

A solution/suspension of Intermediate 20 (100 mg) in phosphorus oxychloride (10 ml) and DMF (0.5 ml) was heated at reflux overnight. The excess phosphorus oxychloride was removed *in vacuo* and ice/water (50 ml) added to the residue. The

aqueous layer was basified using 2M NaOH and extracted with EtOAc (2 x 75 ml). The organic layers were combined, washed with brine (50 ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting solid was purified by column chromatography on silica eluting with 2% MeOH/DCM to afford the desired compound as a yellow solid (40 mg). This was dissolved in dry DMF (10 ml) under nitrogen and to it added the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (38 mg) followed by Na_2CO_3 (35 mg). The reaction mixture was heated at 100°C for 6 hours. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to afford the title compound as a sand-coloured solid (7.6 mg, 5%). LCMS 400/402 $[M+H]^+$, RT 1.90 min. ^1H NMR 300 MHz (d_6-DMSO) 9.98 (1H, s, br), 8.71 (1H, s, br), 8.41 (1H, s), 7.79 (1H, d), 7.61 (1H, d), 7.52 (1H, dd), 7.16 (1H, s, br), 6.49 (1H, t), 4.01-3.80 (3H, m), 3.10-3.00 (2H, m), 2.85-2.70 (2H, m), 1.94-1.82 (2H, m), 1.45-1.30 (2H, m), 0.96 (3H, t).

EXAMPLE 63

tert-Butyl 4-[(5-chloro-4-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}pyrimidin-2-yl)amino]piperidine-1-carboxylate

To a solution/suspension of Intermediate 3 (1.72 g) in dry DMF (75 ml) under nitrogen was added 1-BOC-4-aminopiperidine hydrochloride (4.84 g) and Na_2CO_3 (4.35 g). The mixture was heated at 90°C for 5 hours. The mixture was cooled to room temperature and poured into water (800 ml) and the resulting solid was collected by filtration and dried *in vacuo*. Purification by column chromatography on silica eluting with 5% MeOH/DCM afforded the title compound as a yellow solid (1.23 g, 51%). LCMS 583 $[M+H]^+$, RT 4.94 min. ^1H NMR 300 MHz ($CDCl_3$) 8.80 (1H, s), 8.65 (1H, d), 8.50 (1H, d), 8.30 (1H, s), 8.15 (1H, d), 7.35-7.20 (3H, m), 5.10 (1H, d), 4.20-3.90 (3H, m), 2.95 (2H, t), 2.40 (3H, s), 2.05 (2H, d), 1.55-1.35 (11H, m).

EXAMPLE 64

4-{[5-Chloro-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-2-yl]amino}-*N*,*N*-dimethylpiperidine-1-carboxamide

To a solution of Example 63 (1.0 g) in DCM (20 ml) was added TFA (280 µl) in one portion and the mixture was stirred at room temperature for 4 hours. The solution was then poured into 10% $NaHCO_3$ solution (200 ml) and DCM (100 ml) and stirred rapidly for 1 hour. The organic layer was separated, washed with water (75 ml) and brine (75 ml), and dried over $MgSO_4$. The mixture was filtered and the solvent removed *in*

vacuo to yield a yellow solid (540 mg). To a portion of this solid (100 mg) was added DCM (10 ml), TEA (32 µl) and dimethylcarbamyl chloride (20 µl) and the mixture stirred for 24 hours. The solvent was removed *in vacuo* then MeOH (10 ml) and KOH (100 mg) added and the mixture stirred for a further 24 hours. The solvent was removed *in vacuo*. Purification by column chromatography on silica eluting with 10% MeOH/DCM afforded the title compound as an off-white solid (13.6mg). LCMS 400 $[M+H]^+$, RT 2.66 min. ^1H NMR 300 MHz (d_6-DMSO) 12.40 (1H, s, br), 8.95 (1H, d, br), 8.55 (1H, s), 8.35 (1H, d), 8.30 (1H, s), 7.40 (1H, d), 7.25 (1H, s, br), 3.95 (1H, s), 3.60 (2H, d), 3.35 (2H, t), 3.25 (6H, s), 1.95 (2H, d, br), 1.50 (2H, q).

EXAMPLE 65

tert-Butyl ({4-[(5-chloro-4-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl}pyrimidin-2-yl)amino]piperidin-1-yl}sulfonyl)carbamate

To a solution of Example 63 (1.00 g) in DCM (20 ml) was added TFA (280 µl) in one portion and the mixture was stirred for 4 hours. The solution was then poured into 10% $NaHCO_3$ solution (200 ml) and DCM (100 ml) and stirred rapidly for 1 hour. The organic layer was separated, washed with water (75 ml) and brine (75 ml), and dried over $MgSO_4$. The mixture was filtered and the solvent removed *in vacuo* to yield the desired product (540 mg). To a portion of this solid (433 mg) was added DCM (20 ml) and *N*-(*tert*-butoxycarbonyl)-*N*-[4-(dimethyl-azaniumylidene)-1,4-dihydropyridin-1-ylsulfonyl]azanide (CAS 352275-00-4, 270 mg) and the solution stirred for 24 hours. The solvent was removed *in vacuo*. Purification by column chromatography on silica eluting with 10% MeOH/DCM and then repeated eluting with 50% EtOAc/heptane afforded the title compound as a yellow solid (266 mg). LCMS 662 $[M+H]^+$, RT 4.53 min. ^1H NMR 300 MHz ($CDCl_3$) 8.80 (1H, s), 8.65 (1H, d), 8.50 (1H, d), 8.30 (1H, s), 8.15 (2H, d), 7.30 (2H, d), 7.15 (1H, s), 5.15 (1H, s, br), 4.00 (1H, s, br), 3.85 (2H, d), 3.15 (2H, t), 2.40 (3H, s), 2.15 (2H, d), 1.65 (2H, q), 1.50 (9H, s).

EXAMPLE 66

tert-Butyl 4-{[4-(1*H*-benzimidazol-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

Example 16 (40 mg), EtOAc (10 ml), MeOH (20 ml) and palladium on carbon (10% Pd) (10 mg) were combined and stirred under a hydrogen atmosphere for 36 hours. The catalyst was filtered off and the reaction mixture concentrated *in vacuo*. Purification by column chromatography on silica afforded the title compound as a white solid (7.8 mg, 18%). LCMS 339 $[M-t\text{Bu}]^+$, RT 3.41 min. ^1H NMR 400 MHz (d_6-DMSO, 90°C) 8.95

(1H, s), 8.45 (1H, d), 8.40 (1H, d), 7.75 (1H, d), 7.45-7.30 (2H, m), 7.30-7.15 (1H, m), 7.10 (1H, d), 4.10-3.90 (3H, m), 3.00-2.90 (2H, m), 2.00-1.90 (2H, m), 1.55-1.40 (2H, m), 1.45 (9H, s).

Alternatively, 1-(2-chloropyrimidin-4-yl)-1*H*-benzimidazole (CAS 710328-94-2) (680 mg), 1-BOC-4-aminopiperidine.HCl (698 mg), TEA (1 ml) and DMF (10 ml) were combined under a nitrogen atmosphere and heated to 60°C for 24 hours. The solvents were removed *in vacuo* and the residue triturated with water to give the title compound as an off-white solid (1.4 g, 90%). Identical spectroscopic data.

EXAMPLE 67

4-{[4-(5-Chloro-1*H*-benzimidazol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

Prepared in a similar manner to Example 16 from Intermediate 21 (90 mg) and the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (70.5 mg). Purification by prep HPLC (Method A) afforded the title compound as an off-white solid (42 mg, 31%). LCMS 400/402 $[M+H]^+$, RT 2.67 min. ^1H NMR 300 MHz (d_6-DMSO) 9.20-9.10 (1H, m), 8.80-8.55 (1H, m), 8.45 (1H, d), 7.85-7.70 (2H, m), 7.45-7.35 (1H, m), 7.15 (1H, d), 6.50 (1H, t), 4.10-3.85 (3H, m), 3.10-3.00 (2H, m), 2.95-2.70 (2H, m), 2.00-1.80 (2H, m), 1.50-1.30 (2H, m), 1.00 (3H, t).

EXAMPLE 68

4-{[4-(6-Chloro-1*H*-benzimidazol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

Prepared in a similar manner to Example 16 from Intermediate 22 (90 mg) and the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (70.5 mg). Purification by prep HPLC (Method A) afforded the title compound as an off-white solid (37 mg, 27%). LCMS 400/402 $[M+H]^+$, RT 2.74 min. ^1H NMR 300 MHz (d_6-DMSO) 9.15 (1H, s), 8.80-8.70 (0.5H, m), 8.50-8.40 (1.5H, m), 7.85 (1H, s, br), 7.70-7.35 (3H, m), 7.15 (1H, d), 6.50 (1H, t), 4.05-3.85 (3H, m), 3.10-3.00 (2H, m), 2.95-2.70 (2H, m), 2.00-1.80 (2H, m), 1.50-1.30 (2H, m), 1.00 (3H, t).

EXAMPLE 69

2-(4-{[5-Chloro-4-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide acetate

Intermediate 23 (102 mg), DCM (20 ml) and *m*-CPBA (70-75%) (199 mg) were combined and stirred at room temperature for 16 hours. The solvents were removed *in*

vacuo and the residue dissolved in DMF (5 ml). TEA (0.28 ml) and Intermediate 24 (122 mg) were added to the mixture, which was heated to 80°C for 20 hours. The solvents were removed *in vacuo* and the residue purified by prep HPLC (Method B) to give the title compound as a brown solid (13.8 mg, 9%). LCMS (pH 5.8) 401/403 $[M+H]^+$ (free base), RT 1.37 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.55 (0.5H, br s), 9.25 (0.5H, br s), 8.60 (1H, s), 8.00 (1H, d), 7.90-7.80 (1H, m), 7.70-7.55 (2H, m), 7.20 (1H, t), 3.80-3.60 (1H, m), 2.90 (2H, s), 2.85-2.75 (2H, m), 2.60 (3H, d), 2.20-2.10 (2H, m), 2.00-1.85 (2H, m), 1.85 (3H, s), 1.70-1.50 (2H, m).

EXAMPLE 70

5-Chloro-*N*-[1-(1*H*-imidazol-4-ylcarbonyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

Prepared in similar manner to Example 37 from Example 32 (50 mg) and 4-imidazolecarboxylic acid (26 mg). Purification by prep HPLC (Method A) afforded the title compound as an orange solid (8 mg, 12%). LCMS 422/424 $[M+H]^+$, RT 2.02 min. ^{1}H NMR (400MHz, d_6-DMSO, 110°C) 8.56 (1H, d), 8.39 (1H, s), 8.25 (1H, s), 7.62 (1H, s), 7.52-7.45 (2H, m), 7.24-7.13 (2H, m), 6.78 (1H, d), 4.77-4.63 (2H, m), 4.22-4.11 (1H, m), 3.25-3.15 (2H, m), 2.11-2.02 (2H, m), 1.67-1.55 (2H, m).

EXAMPLE 71

N-[(*S*)-2-{4-[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-ylamino]piperidin-1-yl}-1-(1*H*-imidazol-4-ylmethyl)-2-oxoethyl]acetamide

Prepared in similar manner to Example 37 from Example 32 (50 mg) and *N*-acetyl-L-histidine (45 mg). Purification by prep HPLC (Method A) afforded the title compound as a yellow glass (14 mg, 18%). LCMS 507/509 $[M+H]^+$, RT 1.83 min. ^{1}H NMR (400MHz, d_6-DMSO, 110°C) 8.55 (1H, d), 8.39 (1H, s), 8.24 (1H, s), 8.23 (1H, s), 7.71-7.60 (1H, m), 7.51 (1H, d), 7.46 (1H, s), 7.25-7.13 (2H, m), 6.78-6.70 (2H, m), 5.09-4.99 (1H, m), 4.20-4.01 (3H, m), 2.80-2.65 (2H, m), 2.05-1.95 (2H, m), 1.57-1.35 (2H, m).

EXAMPLE 72

5-Chloro-*N*-[1-(1H-imidazol-2-ylcarbonyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

Prepared in similar manner to Example 37 from Example 32 (60 mg) and 1*H*-imidazole-2-carboxylic acid (31 mg). Purification by prep HPLC (Method A) yielded the title compound as an off-white solid (24 mg, 31%). LCMS 422/424 $[M+H]^+$, RT 2.57

min. ^{1}H NMR (400MHz, d_6-DMSO, 130°C) 8.55 (1H, d), 8.38 (1H, s), 8.25 (1H, s), 7.50 (1H, d), 7.24-7.13 (2H, m), 7.12 (2H, s), 6.69 (1H, d), 5.03-4.85 (2H, m), 4.26-4.15 (2H, m), 3.40-3.29 (2H, m), 2.15-2.08 (2H, m), 1.71-1.60 (2H, m).

EXAMPLE 73

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(pyridin-2-ylacetyl)piperidin-4-yl]pyrimidin-2-amine

To a suspension of the bis HCl salt of Example 32 (30 mg) in dry DCM (5 ml) was added a solution in DCM (5 ml) of EDC.HCl (38 mg), HOBt (2.7 mg) and TEA (0.02 ml) followed by 2-pyridyl acetic acid HCl (17 mg). The reaction was stirred at room temperature overnight and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 10% MeOH/DCM afforded the title compound as a white powder (12.6 mg, 38%). LCMS 447/449 $[M+H]^+$, RT 2.22 min. ^{1}H NMR 300 MHz (d_4 MeOH) 8.61 (1H, d), 8.52-8.47 (2H, m), 8.17 (1H, s), 7.80 (1H, t), 7.48-7.35 (2H, m), 7.30 (1H, t), 7.23-7.12 (2H, m), 4.58-4.48 (1H, m), 4.22-4.07 (2H, m), 4.05-3.98 (1H, m), 3.38-3.28 (2H, m), 3.05-2.92 (1H, m), 2.21-2.08 (2H, m), 1.60-1.40 (2H, m).

EXAMPLE 74

(5*R*)-5-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-2-one

Prepared in similar manner to Example 73 from the bis HCl salt of Example 32 (30 mg) and (*R*)-(+)-2-pyrrolidone-5-carboxylic acid (13 mg). Purification by column chromatography on silica eluting with 10% MeOH/DCM afforded the title compound as an off-white solid (12.8 mg, 39%). LCMS 439/441 $[M+H]^+$, RT 2.48 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.90 (1H, s), 8.65 (1H, s, br), 8.52 (1H, d), 8.31 (1H, s), 7.77 (1H, s), 7.53 (1H, d), 7.41-7.30 (1H, dd), 7.29-7.19 (2H, m), 4.65-4.60 (1H, m), 4.46-4.36 (1H, m), 4.20-4.05 (1H, m), 4.05-3.94 (1H, m), 3.34-3.10 (2H, m), 2.96-2.80 (1H, m), 2.45-2.32 (1H, m), 2.22-2.00 (3H, m), 2.00-1.85 (1H, m), 1.65-1.37 (2H, m).

EXAMPLE 75

tert-Butyl 2-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]-4-hydroxypyrrolidine-1-carboxylate

To a solution of the bis HCl of Example 32 (200 mg) in dry DMF (10 ml) under nitrogen was added EDC.HCl (105 mg) and HOBt (74 mg) and 4-hydroxy-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (127 mg) followed by DIPEA (0.26 ml). The reaction mixture was stirred at room temperature for 4 hours. The mixture was poured into water (200ml) and extracted with EtOAc (2 x 100 ml). The organic layers were

combined, washed with water (50 ml), washed with brine (50 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography on silica eluting with 10% MeOH/DCM afforded the title compound as a yellow solid (168 mg, 63%). LCMS 541 $[M+H]^+$, RT 2.93 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s), 8.62 (1H, s, br), 8.50 (1H, s), 8.29 (1H, s), 7.55-7.40 (2H, m), 7.35-7.10 (2H, m), 5.02 (1H, m), 4.28-4.65 (1H, m), 4.40-4.15 (2H, m), 4.10-3.90 (2H, m), 3.40-3.10 (5H, m), 2.35-2.70 (1H, m), 2.18-1.90 (3H, m), 1.85-1.73 (1H, m), 1.50-1.30 (9H, m).

EXAMPLE 76

4-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]imidazolidin-2-one

Prepared in similar manner to Example 37 from Example 32 (90 mg) and 2-imidazolidone-4-carboxylic acid (54 mg). Purification by column chromatography on silica, eluting with 0-10% MeOH/DCM afforded the title compound as a yellow powder (47 mg, 39%). LCMS 440/442 $[M+H]^+$, RT 2.39 min. ^1H NMR (400MHz, d_6-DMSO, 130°C) 11.40 (1H, s, br), 8.54 (1H, d), 8.37 (1H, s), 8.25 (1H, s), 7.25-7.13 (2H, m), 6.68 (1H, d), 5.81-5.69 (2H. m), 4.61-4.55 (1H, m), 4.20-4.01 (3H, m), 3.69-3.61 (1H, m), 3.42-3.37 (1H, m), 3.19-3.05 (2H, m), 2.11-2.01 (2H, m), 1.66-1.51 (2H, m).

EXAMPLES 77 and 78

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(tetrahydrofuran-3-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

Prepared in similar manner to Example 73 from Example 32 (50 mg) and tetrahydro-3-furoic acid (16 mg). Purification by column chromatography on silica eluting with 10% MeOH/DCM gave a racemic mixture of the title compounds. Separation of the two enantiomers was achieved using chiral prep HPLC. (Mobile phase: 75% EtOH, 25% heptane, flow rate: 9 ml/min, run time 35 min.) Enantiomer 1 was afforded as a white solid (18 mg, 28%). Chiral HPLC (Mobile phase: 60% EtOH, 40% heptane, flow rate: 1 ml/min, run time: 30 min) RT 8.55 min. ^1H NMR 400 MHz ($CDCl_3$) 8.61 (1H, s), 8.59 (1H, d), 8.40 (1H, d), 8.25 (1H, s), 7.45 (1H, d), 7.30-7.22 (2H, m), 5.08 (1H, d), 4.58 (1H, d), 4.20 (1H, s, br), 4.02 (1H, t), 3.99-3.83 (4H, m), 3.30-3.23 (2H, m), 2.98-2.89 (1H, m), 2.30-2.05 (4H, m), 1.50-1.40 (2H, m). Enantiomer 2 was afforded as a white solid (18 mg, 28%). Chiral HPLC, RT 10.39 min. ^1H NMR 400 MHz ($CDCl_3$) 8.61 (1H, s), 8.59 (1H, d), 8.40 (1H, d), 8.25 (1H, s), 7.45 (1H, d), 7.30-7.22

(2H, m), 5.08 (1H, d), 4.58 (1H, d), 4.20 (1H, s, br), 4.02 (1H, t), 3.99-3.83 (4H, m), 3.30-3.23 (2H, m), 2.98-2.89 (1H, m), 2.30-2.05 (4H, m), 1.50-1.40 (2H, m).

EXAMPLE 79

3-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]cyclopentanone

Prepared in similar manner to Example 73 from Example 32 (100 mg) and 3-oxo-cyclopentane-1-carboxylic acid (77 mg). Purification by column chromatography on silica eluting with 10% MeOH/DCM furnished the title compound as a yellow oil (84 mg, 63%). LCMS 438/440 $[M+H]^+$, RT 2.90 min. ^{1}H NMR (300MHz, d_6-DMSO) 8.71-8.53 (1H, m, br), 8.49 (1H, s), 8.29 (1H, s), 7.53-7.48 (1H, m), 7.35-7.14 (3H, m), 4.44-4.34 (1H, m), 4.15-3.99 (2H, m), 3.59-3.46 (1H, m), 3.30-3.26 (1H, m), 2.89-2.0 (1H, m), 2.42-1.83 (8H, m), 1.56-1.32 (2H, m).

EXAMPLE 80

(5*S*)-5-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-2-one

Prepared in similar manner to Example 73 from the TFA salt of Example 32 (50 mg) and (*S*)-(-)-2-pyrrolidone-5-carboxylic acid (15 mg). Purification by column chromatography on silica eluting with 10% MeOH/DCM gave the title compound as an off-white solid (23.8 mg, 48%). LCMS 439/441 $[M+H]^+$, RT 2.49 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s), 8.60 (1H, s, br), 8.50 (1H, d), 8.27 (1H, s), 7.73 (1H, s), 7.50 (1H, d), 7.40-7.28 (1H, dd), 7.25-7.12 (2H, m), 4.60-4.53 (1H, m), 4.40-4.30 (1H, m), 4.12-3.87 (2H, m), 3.25-3.13 (1H, m), 2.90-2.72 (1H, m), 2.40-2.25 (1H, m), 2.17-1.90 (4H, m), 1.90-1.80 (1H, m), 1.55-1.32 (2H, m).

EXAMPLES 81 and 82

4-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]cyclohexanol

Prepared in similar manner to Example 73 from 5-chloro-4-(1*H*-indol-3-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (100 mg) and 4-hydroxycyclohexanecarboxylic acid (45 mg). Purification was achieved by prep HPLC (Method C). Example 81 was afforded as a white solid (2.4 mg, 2%). LCMS 454/456 $[M+H]^+$, RT 2.66min. ^{1}H NMR (400MHz, d_4-MeOH) 8.65 (1H, d), 8.50 (1H, s), 8.20 (1H, s), 7.49 (1H, d), 7.28-7.18 (2H, m), 4.43 (1H, s), 4.59-4.51 (1H, m), 4.26-4.09 (2H, m), 3.60-3.50 (1H, m), 2.95-2.85 (1H, m), 2.71-2.62 (2H, m), 2.29-2.10 (2H, m), 2.06-1.97 (2H, m), 1.87-1.77 (2H, m), 1.65-

1.45 (4H, m), 1.42-1.28 (2H, m). Example 82 was afforded as a yellow solid (22.4 mg, 16%): LCMS 454/456 $[M+H]^+$, RT 2.84 min. ^1H NMR (400MHz, d_4-MeOH) 8.64 (1H, d), 8.49 (1H, s), 8.18 (1H, s), 7.47 (1H, d), 7.27-7.16 (2H, m), 4.59-4.49 (1H, m), 4.25-4.05 (2H, m), 3.98 (1H, s, br), 3.32-3.20 (1H, m), 2.95-2.82 (1H, m), 2.78-2.69 (1H, m), 2.27-2.09 (2H, m), 2.01-1.79 (4H, m), 1.69-1.41 (6H, m), 1.36-1.27 (1H, m).

EXAMPLE 83

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(4-methoxycyclohexyl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

Prepared in similar manner to Example 73 from the bis HCl salt of Example 32 (30 mg) and 4-methoxycyclohexane carboxylic acid (13 mg). Purification by column chromatography on silica eluting with EtOAc/heptane afforded the title compound as an off-white powder (12.6 mg, 36%). LCMS 468/470 $[M+H]^+$, RT 3.36 min. 1H NMR (400MHz, d_4-MeOH) 8.53 (1H, dd), 8.39 (1H, s), 8.09 (1H, s), 7.37 (1H, dd), 7.16-7.05 (2H, m), 4.49-4.39 (1H, m), 4.15-3.95 (2H, m), 3.42-3.34 (1H, m), 3.21 (s, 3H), 2.85-2.73 (1H, m), 2.70-2.59 (1H, m), 2.19-1.98 (2H, m), 1.96-1.84 (2H, m), 1.81-1.63 (2H, m), 1.54-1.31 (5H, m).

EXAMPLE 84

Methyl (3*R*)-4-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-3-methyl-4-oxobutanoate

Prepared in similar manner to Example 73 from 5-chloro-4-(1*H*-indol-3-yl)-*N*-(piperidin-4-yl)pyrimidin-2-amine (150 mg) and (*R*)-(+)-methylsuccinic acid 4-methyl ester (76 µl). Purification by prep HPLC (Method C) afforded the title compound as a yellow oil (9.4 mg, 6.8%). LCMS 456/458 $[M+H]^+$, RT 3.16 min. 1H NMR (400MHz, d_4-MeOH) 8.65 (1H, d), 8.5 (1H, s), 8.20-8.10 (2H, m), 7.45 (1H, d), 7.30-7.15 (2H, m), 4.60-4.40 (1H, m), 4.30-4.10 (2H, m), 3.68 (3H, d), 3.40-3.25 (3H, m), 3.05-2.73 (2H, m), 2.40 (1H, dd), 2.35-2.05 (2H, m), 1.70-1.42 (2H, m), 1.20-1.10 (3H, m).

EXAMPLE 85

4-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]-1,3-oxazolidin-2-one

Prepared in similar manner to Example 73 from the bis TFA salt of Example 32 (150 mg) and 2-oxo-oxazolidine-4-carboxylic acid (53 mg). Purification by column chromatography on silica eluting with 5% MeOH/DCM yielded the title compound as a yellow solid (48 mg, 40%). LCMS 441/443 $[M+H]^+$, RT 2.57 min. ^1H NMR (300MHz,

d_6-DMSO) 8.75-8.50 (1H, m), 8.50-8.45 (1H, m), 8.27 (1H, s), 8.00-7.90 (1H, m), 7.50 (1H, d), 7.40-7.12 (3H, m), 4.89-4.79 (1H, m), 4.56-4.45 (1H, m), 4.40-4.20 (2H, m), 4.15-3.95 (1H, m), 3.88-3.72 (1H, m), 3.29-3.09 (1H, m), 2.95-2.79 (1H, m), 2.14-1.90 (2H, m), 1.61-1.32 (2H, m).

EXAMPLES 86-110

Examples 86-112 were prepared using parallel synthesis techniques as described below. The bis HCl salt of Example 32 (1.65 g) was dissolved in DCM (55 ml). A portion of this solution (1 ml) was dispensed into the 48 wells of one Whatman 48 deep well plate and 7 wells of another. Solutions of the appropriate carboxylic acid (0.5 M in NMP) (200 µl) were added to the individual wells. A solution of EDC.HCl (0.2 M in DCM) (500 µl) and a solution of HOBt (0.2 M in DCM) (50 µl) were added to each well and the plate shaken for 72 hours. The solvents were removed *in vacuo* and DMSO (1 ml) added to each well. The desired products from each well were isolated by prep HPLC (Method A) to yield on average 10 mg of the title compounds.

EXAMPLE 86

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(3-thienylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

The title compound was isolated as an off-white solid (9.3 mg). LCMS 438/440 $[M+H]^+$, RT 3.35 min. ^{1}H NMR 300 MHz ($CDCl_3$) 8.69 (1H, s), 8.58 (1H, d), 8.40 (1H, s), 8.23 (1H, d), 7.52 (1H, m), 7.42 (1H, d), 7.38-7.18 (4H, m), 5.10 (1H, d), 4.70-4.53 (1H, m), 4.30-4.12 (1H, m), 3.30-3.10 (2H, m), 2.30-2.18 (2H, m), 1.65-1.45 (2H, m).

EXAMPLE 87

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(2-thienylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

The title compound was isolated as an off-white solid (11 mg). LCMS 438/440 $[M+H]^+$, RT 3.45 min. ^{1}H NMR 300 MHz ($CDCl_3$) 8.69 (1H, s), 8.58 (1H, d), 8.40 (1H, d), 8.25 (1H, s), 7.48-7.42 (2H, m), 7.32-7.22 (3H, m), 7.08-7.03 (1H, m), 5.12 (1H, d), 4.50-4.38 (2H, m), 4.30-4.16 (1H, m), 3.30-3.18 (2H, m), 2.30-2.20 (2H, m), 1.65-1.50 (2H, m).

EXAMPLE 88

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(1,3-thiazol-4-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

The title compound was isolated as an off-white solid (5.4 mg). LCMS 439/441 $[M+H]^+$, RT 2.94 min. ^{1}H NMR 300 MHz ($CDCl_3$) 8.80 (1H, d), 8.70 (1H, s, br), 8.59 (1H, d), 8.40 (1H, s), 8.21 (1H, s), 7.99 (1H, d), 7.45 (1H, dd), 7.35-7.22 (2H, m), 5.60

(1H, s, br), 4.70-4.60 (1H, m), 4.50-4.40 (1H, m), 4.30-4.20 (1H, m), 3.45-3.32 (1H, m), 3.20-3.10 (1H, m), 2.40-2.15 (2H, m), 1.68-1.50 (2H, m).

EXAMPLE 89

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(2-methyl-1,3-thiazol-4-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 453/455 $[M+H]^+$, RT 3.11 min.

EXAMPLE 90

6-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]-4,5-dihydropyridazin-3(2*H*)-one

LCMS 452/454 $[M+H]^+$, RT 2.62 min.

EXAMPLE 91

5-Chloro-*N*-[1-(cyclopentylcarbonyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 424/426 $[M+H]^+$, RT 3.64 min.

EXAMPLE 92

N-(1-Benzoylpiperidin-4-yl)-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 432/434 $[M+H]^+$, RT 3.44 min.

EXAMPLE 93

5-Chloro-*N*-[1-(cyclopropylcarbonyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 396/398 $[M+H]^+$, RT 3.14 min.

EXAMPLE 94

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(pyridin-3-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 433/435 $[M+H]^+$, RT 2.68 min.

EXAMPLE 95

N-{1-[3-(1*H*-Benzimidazol-2-yl)propanoyl]piperidin-4-yl}-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 500/502 $[M+H]^+$, RT 2.21 min.

EXAMPLE 96

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-propionylpiperidin-4-yl)pyrimidin-2-amine

LCMS 384/386 $[M+H]^+$, RT 3.02 min.

EXAMPLE 97

5-Chloro-*N*-[1-(2,2-dimethylpropanoyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 412/414 $[M+H]^+$, RT 3.58 min.

EXAMPLE 98

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(1,8-naphthyridin-2-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 484/486 $[M+H]^+$, RT 2.80 min.

EXAMPLE 99

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(2-methylbenzoyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 446/448 $[M+H]^+$, RT 3.59 min.

EXAMPLE 100

4-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-4-oxobutanamide

LCMS 427/429 $[M+H]^+$, RT 2.41 min.

EXAMPLE 101

5-Chloro-*N*-[1-(cinnolin-4-ylcarbonyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 484/486 $[M+H]^+$, RT 1.81 min.

EXAMPLE 102

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-isobutyrylpiperidin-4-yl)pyrimidin-2-amine

LCMS 398/400 $[M+H]^+$, RT 3.26 min.

EXAMPLE 103

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(3-methylbenzoyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 446/448 $[M+H]^+$, RT 3.66 min.

EXAMPLE 104

N-[1-(2*H*-1,2,3-benzotriazol-2-ylacetyl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 487/489 $[M+H]^+$, RT 3.41 min.

EXAMPLE 105

3-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]-5,6-dimethylpyridin-2(1*H*)-one

LCMS 477/479 $[M+H]^+$, RT 2.64 min.

EXAMPLE 106

N-[1-(1*H*-Benzimidazol-5-ylcarbonyl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 472/474 $[M+H]^+$, RT 2.15 min.

EXAMPLE 107

N-[1-(1*H*-Benzimidazol-2-ylcarbonyl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 472/474 $[M+H]^+$, RT 3.33 min.

EXAMPLE 108

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(1-methyl-1*H*-pyrazol-5-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 436/438 $[M+H]^+$, RT 2.97 min.

EXAMPLE 109

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(2-phenylpropanoyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 460/462 $[M+H]^+$, RT 3.76 min.

EXAMPLE 110

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(tetrahydro-3-thienylacetyl)piperidin-4-yl]pyrimidin-2-amine

A solution of the bis HCl salt of Example 32 (192 mg), (tetrahydrothiophen-3-yl)acetic acid (127 mg), HBTU (181 mg) and TEA (1 mL) in DMF (10 mL) was stirred at r.t. for 18 hours. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to afford the title compound as a pale gold coloured solid (63 mg, 29%). LCMS 456/458 $[M+H]^+$, RT 3.48 min. ^{1}H NMR (300MHz, d_6-DMSO) 11.86 (1H, s, br), 8.71-8.52 (1H, m), 8.48 (1H, d), 8.29 (1H, s), 7.49 (1H, d), 7.31 (1H, d), 7.25-7.14 (2H, m), 4.45-4.34 (1H, m), 4.11-3.89 (2H, m), 3.24-3.09 (1H, m), 2.98-2.78 (1H, m), 2.85-2.69 (3H, m), 2.52-2.40 (4H, m), 2.15-1.90 (3H, m), 1.65-1.30 (3H, m).

EXAMPLES 111 and 112

3-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]cyclopentanol

Sodium borohydride (30 mg) was added to a solution of Example 79 (30 mg) in MeOH (5 ml) and MeCN (5 ml). The reaction mixture was stirred at r.t. for 10 min and then quenched with water (10 ml). The solvents were removed *in vacuo*. Purification was achieved by prep HPLC (Method C). Example 111 was afforded as a white solid (3 mg, 10%). LCMS 440/442 $[M+H]^+$, RT 2.65 min. ^{1}H NMR (400MHz, d_4-MeOH) 8.65 (1H, d), 8.49 (1H, s), 8.20 (1H, s), 7.49 (1H, d), 7.28-7.17 (2H, m), 4.91 (1H, s), 4.59-4.51 (1H, m), 4.41-4.35 (1H, m), 4.27-4.11 (2H, m), 3.44-3.33 (2H, m), 3.00-2.88 (1H, m), 2.29-1.90 (5H, m), 1.90-1.74 (2H, m), 1.72-1.44 (3H, m). Example 112 was afforded as a

white solid (20 mg, 66%): LCMS 440/442 $[M+H]^+$, RT 2.84 min. ^1H NMR (400MHz, d_4-MeOH) 8.64 (1H, d), 8.49 (1H, s), 8.19 (1H, s), 7.48 (1H, d), 7.27-7.16 (2H, m), 4.90 (1H, s), 4.59-4.49 (1H, m), 4.29-4.08 (3H, m), 3.37-3.18 (2H, m), 3.00-2.89 (1H, m), 2.28-2.08 (3H, m), 2.01-1.79 (4H, m), 1.78-1.68 (1H, m), 1.62-1.45 (2H, m).

EXAMPLE 113

(3*R*)-4-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-3-methyl-4-oxobutanoic acid

To a solution of Example 84 in water/THF (5 ml/5 ml) was added $LiOH.H_2O$ (45.6 mg). The reaction mixture was stirred at r.t. for 2 hours and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 0-10% MeOH/EtOAc yielded the title compound as a lemon yellow solid (163 mg, 100%). LCMS 442/444 $[M+H]^+$, RT 2.77 min. ^1H NMR (300MHz, d_6-DMSO) 11.85 (1H, s, br), 8.45 (1H, d), 8.28 (1H, s), 7.53-7.40 (1H, m), 7.40-7.35 (1H, m), 7.35-7.10 (2H, m), 4.52-4.30 (1H, m), 4.20-3.90 (2H, m), 3.30-3.10 (2H, m), 2.9-2.7 (1H, m), 2.65-2.55 (1H, m), 2.15-1.90 (2H, m), 1.65-1.30 (2H, m), 1.05-0.95 (3H, m).

EXAMPLE 114

(3*R*)-4-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-3-methyl-4-oxobutan-1-ol

To a solution of Example 84 (227 mg) in dry DCM under nitrogen (5 ml) cooled to –78°C was added slowly over a period of 15 min diisobutylaluminium hydride (1.5 M in toluene) (1 ml). The reaction mixture was stirred for a further hour at –78°C. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to afford the title compound as an orange oil (5.2 mg, 2.3%). LCMS 428/430 $[M+H]^+$, RT 2.96 min (pH 5.8). ^1H NMR (300MHz, d_6-DMSO) 11.85 (1H, s, br), 8.50 (1H, s), 7.5 (1H, d), 7.35-7.10 (3H, m), 4.45-4.35 (2H, m), 4.15-3.95 (2H, m), 3.45-2.60 (4H, m), 2.55 (1H, s), 2.10-1.80 (2H, m), 1.55-1.25 (3H, m), 1.05-0.95 (3H, m).

EXAMPLE 115

Formic acid - 5-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-3-ol (1:1)

To a suspension of Example 75 (128 mg) in DCM (5 ml) was added TFA (52 µl) and the reaction mixture was stirred at r.t. for 24 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on reverse phase silica eluting with 0-60% (MeOH + 0.04% formic acid)/(H_2O + 0.04% formic acid). The solvent was

removed *in vacuo* and the residue triturated with MeOH/Et_2O to afford the title compound as a white solid (63.3 mg, 100%). LCMS 439/ 441 $[M+H]^+$ (Free base), RT 1.91 min. ^1H NMR (300MHz, d_6-DMSO) 11.90 (1H, s, br), 8.65-8.55 (1H, m), 8.50 (1H, d), 8.30 (1H, s), 7.50 (1H, d), 7.37 (1H, dd), 7.28-7.10 (2H, m), 5.50-5.20 (1H, m), 4.68-4.50 (1H, m), 4.42-4.27 (2H, m), 4.20-3.98 (1H, m), 3.98-3.78 (1H, m), 3.30-3.10 (2H, m), 3.05-2.70 (2H, m), 2.35-1.75 (4H, m), 1.65-1,30 (2H, m).

EXAMPLE 116

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(piperidin-4-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

To a solution of the bis HCl salt of Example 32 (1 g) in DMF (50 ml) was added BOC-isonipecotic acid (573 mg), EDC.HCl (620 mg), HOBt (439 mg) and TEA (697 µl). The reaction mixture was stirred overnight at r.t.. The solvent was removed *in vacuo* to afford a yellow solid (1.6 g, 100%). This was suspended in a solution of HCl (1M in Et_2O) (100 ml) and the reaction mixture stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 0-40% MeOH/DCM to afford the title compound as a sunshine yellow solid (798 mg, 61%). LCMS 439/441 $[M+H]^+$, RT 1.96 min. ^1H NMR (300MHz, d_6-DMSO) 8.80-8.35 (3H, m), 7.50 (1H, d), 7.45-7.30 (1H, m), 7.25-7.15 (2H, m), 4.45-4.30 (1H, m), 4.15-4.00 (2H, m), 3.60-3.20 (5H, m), 3.10-3.35 (3H, m), 2.15-1.85 (2H, m), 1.82-1.65 (3H. m), 1.60-1.30 (2H, m).

EXAMPLE 117

4-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]-*N*-ethylpiperidine-1-carboxamide

To a solution of Example 116 (100 mg) in DCM (10 ml) was added ethyl isocyanate (17.4 µl). The reaction mixture was stirred overnight at r.t. and the solvent was removed *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as a matt gold solid (21.1 mg, 18%). LCMS (pH 5.8) 510/512 $[M+H]^+$, RT 3.04 min. ^1H NMR (300MHz, d_6-DMSO) 11.85 (1H, s, br), 8.72-8.52 (1H, m), 8.48 (1H, d), 8.28 (1H, s), 7.50 (1H, d), 7.30 (1H, d), 7.28-7.10 (2H, m), 6.42 (1H, t), 4.45-4.32 (1H, m), 4.15-3.87 (5H, m), 3.28-3.10 (1H. m), 3.05 (2H, q), 2.90-2.62 (5H, m), 2.10-1.88 (2H. m), 1.63-1.28 (4H, m), 1.00 (3H, t).

EXAMPLE 118

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-{[1-(methylsulfonyl)piperidin-4-yl]carbonyl}piperidin-4-yl)pyrimidin-2-amine

To a solution of Example 116 (100mg) in DCM (10 ml) was added methane sulphonyl chloride (17.02 µl) and TEA (63.6 µl). The reaction mixture was stirred at r.t. overnight and the solvent was removed *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as a dark orange solid (2.1 mg, 1.8%). LCMS (pH 5.8) 517/519 $[M+H]^+$, RT 3.21 min. ^{1}H NMR (300MHz, d_6-DMSO) 11.85 (1H, s, br), 8.68-8.52 (1H, m), 8.48 (1H, d), 8.28 (1H, s), 7.50 (1H, d), 7.30 (1H, d), 7.28-7.10 (2H, m), 4.45-4.32 (1H, m), 4.15-3.98 (2H, m), 3.60-3.50 (2H. m), 3.30-3.10 (1H, m), 2.85 (3H, s), 2.85-2.70 (4H, m), 2.12-1.90 (2H, m), 1.80-1.20 (6H, m).

EXAMPLE 119

2-{4-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]piperidin-1-yl}-*N*-methylacetamide

To a solution of Example 116 (100 mg) in DCM (10 ml) was added 2-chloro-N-methylacetamide (23.7 mg) and TEA (63.6 µl). The reaction mixture was stirred for 3 days at r.t. and the solvent was removed *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as a dark orange solid (18.3 mg, 16%). LCMS (pH 5.8) 510/512 $[M+H]^+$, RT 2.87 min (pH 5.8). ^{1}H NMR (300MHz, d_6-DMSO) 11.85 (1H, s, br), 8.70-8.52 (1H, m), 8.48 (1H, d), 8.28 (1H, s), 7.68 (1H, d), 7.50 (1H, d), 7.30 (1H, s), 7.28-7.10 (2H, m), 4.45-4.32 (1H, m), 4.15-3.90 (2H, m), 3.28-3.05 (1H. m), 2.85 (2H, s), 2.83-2.68 (3H, s), 2.60 (3H, d), 2.10-1.28 (11H, m).

EXAMPLE 120

tert-Butyl 4-[(4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidine-1-carboxylate

To a suspension/solution of 4-amino-1-*tert*-butoxycarbonyl piperidine (1.0 g) in dry MeCN (20 ml) under nitrogen was added TEA (1.7 ml) followed by 3,5-dimethyl-pyrazole-1-carboxamidine nitrate (1.1 g). The reaction mixture was heated at 60°C overnight. The reaction mixture was allowed to cool to r.t. and the solvent removed *in vacuo* to afford a light orange viscous oil. This was dissolved in dry DMF (20 ml) under nitrogen at 40°C and NaH (60% dispersion in mineral oil, 0.4 g) was added in a single portion. After stirring for 5 min, *N*-[(*E*)-2-imidazo[1,2-a]pyridin-3-ylvinyl]-*N,N*-dimethylamine (CAS 328062-30-2) (0.54 g) was added and the reaction mixture was

heated at 100°C overnight. The mixture was allowed to cool to r.t., water (50 ml) was added and the mixture extracted with EtOAc (200 ml). The organic layer was washed with water (6 x 30 ml), washed with brine (30ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Trituration in Et_2O afforded the title compound as a cream solid (0.58 g, 59%). LCMS 395 $[M+H]^+$, RT 2.29 min. ^1H NMR 300 MHz (d_6-DMSO) 10.3-9.8 (1H, m, br), 8.55 (1H, s), 8.37 (1H, d), 7.75 (1H, d), 7.47 (1H, t), 7.35 (1H, d), 7.25-7.07 (1H, m, br), 7.15 (1H, d), 4.05-3.85 (3H, m), 3.10-2.80 (2H, m), 2.00-1.85 (2H, m), 1.50-1.30 (2H, m), 1.40 (9H, s).

EXAMPLE 121

4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidine tris(hydrochloride)

To a solution of Example 120 (75 mg) in MeOH / DCM (10 ml / 5 ml) was added HCl (2.0M in Et2O) (3.8 ml). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo* to afford the title compound as a yellow solid (90 mg, quantitative). LCMS (pH 5.8) 295 $[M+H]^+$, RT 1.59 min. ^1H NMR 300 MHz (d_6-DMSO) 10.55-9.85 (1H, m, br), 9.4-8.85 (3H, m), 8.5-8.3 (2H, m), 8.25-7.90 (2H, m), 7.70-7.45 (1H, m), 7.45-7.30 (1H, m), between 5.0 and 3.5 obscured by water peak (1H), 3.50-3.25 (2H, m), 3.25-2.80 (2H, m), 2.20-2.00 (2H, m), 1.90-1.65 (2H, m).

EXAMPLE 122

4-Imidazo[1,2-a]pyridin-3-yl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

Prepared in similar manner to Example 73 from Example 121 (100 mg) and tetrahydro-2*H*-pyran-4-carboxylic acid (CAS 5337-03-1) (48 mg). Purification by trituration in DCM/Et_2O afforded the title compound as a cream solid (51 mg, 51%). LCMS 407 $[M+H]^+$, RT 1.61 min. ^1H NMR (300MHz, d_6-DMSO) 10.25-9.90 (1H, m), 8.52 (1H, s), 8.28 (1H, d), 7.78 (1H, d), 7.50-7.42 (2H, m), 7.38 (1H, d), 7.18 (2H, d), 4.40-4.30 (1H, m), 4.10-3.95 (2H, m), 3.90-3.30 (2H. m), 3.45-3.30 (2H, m), 3.20-3.10 (1H, m), 3.00-2.70 (2H, m), 2.10-1.90 (2H, m), 1.70-1.25 (6H, m).

EXAMPLE 123

(5*S*)-5-({4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}carbonyl)pyrrolidin-2-one

Prepared in similar manner to Example 73 from Example 121 (100 mg) and (*S*)-(-)-2-pyrrolidone-5-carboxylic acid (44 mg). Purification by trituration in DCM/Et_2O afforded the title compound as a lemon yellow solid (48 mg, 52%). LCMS 406 $[M+H]^+$,

RT 1.38 min. ^{1}H NMR (300MHz, d_6-DMSO) 10.25-9.90 (1H, m), 8.52 (1H, s), 8.28 (1H, d), 7.78 (1H, d), 7.50-7.35 (2H, m), 7.15 (2H, d), 4.65-4.58 (1H, m), 4.38-4.25 (1H, m), 4.15-3.85 (2H, m), 3.30-3.10 (1H. m), 3.00-2.75 (1H, m), 2.45-2.25 (1H, m), 2.20-1.75 (5H, m), 1.60-1.25 (1H, m).

EXAMPLE 124

Acetic acid - *N*-(2-({4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-2-oxoethyl)-acetamide (1:1)

To a solution of Example 121 (100 mg) in DCM (5 ml) and DMF (2ml) was added *N*-acetylglycine (32 mg), HBTU (100 mg) and DIPEA (240 µl). The reaction mixture was stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue partitioned between water (50 ml) and EtOAc (50 ml). Precipitation was observed and the solvent from the organic layer was removed *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as a brown solid (40 mg, 44%). LCMS (pH 5.8) 394 $[M+H]^+$ (Free base), RT 2.07 min (pH 5.8). ^{1}H NMR (300MHz, d_4-MeOH) 10.15-10.05 (1H, m), 8.40 (1H, s), 8.22 (1H, d), 7.70 (1H, d), 7.50 (1H, dd), 7.20-7.08 (2H, m), 4.55-4.45 (1H, m), 4.22-3.90 (4H, m), 3.40-3.25 (1H, m), 3.08-2.92 (1H. m), 2.25-1.95 (8H, m), 1.70-1.45 (2H, m).

EXAMPLE 125

4-Imidazo[1,2-a]pyridin-3-yl-*N*-[1-(tetrahydrofuran-3-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

Prepared in similar manner to Example 124 from Example 121(175 mg) and tetrahydrofuoric acid (20 µl). Purification by column chromatography on reverse phase silica eluting with 0-60% (MeOH + 0.04% formic acid)/(H_2O + 0.04% formic acid) afforded the title compound as a brown solid (48 mg, 64%). LCMS 393 $[M+H]^+$, RT 1.55 min. ^{1}H NMR (300MHz, d_4-MeOH) 10.18 (1H, s, br), 8.42 (1H, s), 8.28 (1H, d), 7.72 (1H, d), 7.60-7.50 (1H, m), 7.22-7.10 (2H, m), 4.55-4.45 (1H, m), 4.22-4.09 (2H, m), 4.09-3.78 (4H, m), 3.58-3.45 (1H. m), 3.45-3.28 (1H, m), 3.08-2.92 (1H, m), 2.28-2.07 (4H, m), 1.68-1.45 (2H, m).

EXAMPLE 126

5-Chloro-4-imidazo[1,2-a]pyridin-3-yl-*N*-piperidin-4-ylpyrimidin-2-amine tris(hydrochloride)

To a solution of 3-(2,5-dichloropyrimidin-4-yl)imidazo[1,2-a]pyridine (1.81 g) in dry DMF (30 ml) under nitrogen was added 4-amino-1-BOC-piperidine (1.37 g) and TEA

(2.1 ml). The reaction mixture was heated at reflux for 6 hours. After cooling to r.t. the solvent was removed *in vacuo* and the residue purified by column chromatography on silica eluting with 0-100% EtOAc/heptane followed by trituration in water to afford an off-white solid. This was dissolved in MeOH (20 ml) and to it added a solution of HCl (2M in Et_2O) (20 ml). The mixture was stirred at r.t. overnight and most of the solvent removed *in vacuo*. The resulting solid was collected by filtration to afford the title compound as an off-white solid (200 mg, 9%). LCMS 329/331 $[M+H]^+$, RT 1.20 min. ^1H NMR 300 MHz (d_6-DMSO) 10.1 (1H, s, br), 8.80 (1H, m, br), 8.56 (1H, s), 8.04-7.85 (2H, m), 7.65-7.35 (3H, m), 4.10-3.90 (1H, m), 3.40-3.25 (2H, m), 3.10-2.90 (2H, m), 2.15-2.02 (2H, m), 1.83-1.67 (2H, m).

EXAMPLE 127

N-(2-({4-[(5-Chloro-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-2-oxoethyl)-acetamide,

Prepared in similar manner to Example 73 from Example 126 (50 mg) and *N*-acetylglycine (13.4 mg). Precipitation from EtOAc/aqueous sodium bicarbonate solution afforded the title compound as a yellow solid (25 mg, 51%). LCMS 428/430 $[M+H]^+$, RT 1.72 min. ^1H NMR (300MHz, d_6-DMSO) 10.05-9.6 (1H, m), 8.75-8.60 (1H, m), 8.42 (1H, s), 8.03 (1H, m), 7.85-7.05 (5H, m), 4.38-4.25 (1H, m), 4.08-3.78 (4H, m), 3.25-3.05 (1H, m), 2.98-2.72 (1H, m), 2.05-1.80 (5H. m), 1.60-1.25 (2H, m).

EXAMPLE 128

5-Chloro-4-imidazo[1,2-a]pyridin-3-yl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

Prepared in similar manner to Example 73 from Example 126 (50 mg) and tetrahydro-2*H*-pyran-4-carboxylic acid (CAS 5337-03-1) (15 mg). Precipitation from EtOAc/Et_2O afforded the title compound as a yellow solid (50 mg, 95%). LCMS 441/443 $[M+H]^+$, RT 2.00 min. ^1H NMR (300MHz, d_6-DMSO) 9.09 (1H, m), 8.75-8.60 (1H, m), 8.42 (1H, s), 7.85-7.40 (4H, m), 7.30-7.05 (1H, m), 4.42-4.28 (1H, m), 4.10-3.90 (2H, m), 3.90-3.80 (2H, m), 3.30-2.68 (3H, m), 2.08-1.88 (2H, m), 1.70-1.20 (6H. m).

EXAMPLE 129

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(pyridin-2-ylmethyl)sulfonyl]piperidin-4-yl}pyrimidin-2-amine

To a solution of Example 32 (100 mg) in dry MeCN (10 ml) under nitrogen was added (2-pyridylmethyl)sulfonyl chloride triflate (115 mg) and TEA (0.134 ml). The

mixture was stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica eluting with 20% EtOAc/heptane to afford the title compound as an ivory powder (8.5 mg, 5.8%). LCMS 483/485 $[M+H]^+$, RT 3.19 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.9-11.82 (1H, s, br), 8.67-8.59 (1H, d), 8.48 (1H, d), 8.4 (1H, d), 8.4-8.3 (1H, t), 7.6-7.45 (2H, m), 7.45-7.37 (2H, m), 7.35-7.3 (1H, d), 7.3-7 (2H, m), 4.65-4.52 (2H, s), 3.9-3.75 (1H, m), 3.65-3.5 (2H, d), 2.93-2.78 (2H, t), 2.1-1.9 (2H, m), 1.6-1.4 (2H, m).

EXAMPLE 130

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(pyridin-4-ylmethyl)sulfonyl]piperidin-4-yl}pyrimidin-2-amine

Prepared in similar manner to Example 129 from the bis HCl salt of Example 32 (150 mg) and (4-pyridylmethyl)sulfonyl chloride triflate (128 mg). Purification by prep HPLC (Method A) afforded the title compound as a gold solid (13 mg, 7%). LCMS 483/485 $[M+H]^+$, RT 3.33 min. ^{1}H NMR 300 MHz (d_6-DMSO) 8.65-8.58 (3H, d), 8.5 (1H, d), 8.28 (1H, s), 7.5-7.42 (3H, d), 7.4-7.3 (1H, d), 7.3-7.15 (1H, m), 4.55 (2H, s), 3.7-3.55 (2H, d), 2.97-2.82 (3H, t), 2.12-1.9 (2H, m), 1.6-1.4 (2H, m).

EXAMPLE 131

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(isopropylsulfonyl)piperidin-4-yl]pyrimidin-2-amine

To a solution of 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1*H*-indole (100 mg) in DMF (1.5 ml) was added 1-(isopropylsulfonyl)piperidin-4-amine hydrochloride (72 mg) and Na_2CO_3 (87 mg). The reaction mixture was heated to 95°C for 5 hours and then left to cool overnight. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (30 ml). The organic layer was washed with water (10 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow solid was dissolved in MeOH (4.5 ml) and to this added KOH (19 mg). The reaction mixture was stirred at r.t. for 3 hours and the solvent removed *in vacuo*. Purification by prep HPLC (Method A) afforded the title compound as a yellow solid (27 mg, 25%). LCMS 434/436 $[M+H]^+$, RT 3.50 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.80-8.50 (1H, s, br), 8.50 (1H, s), 8.30 (1H, s), 7.52-7.48 (1H, d), 7.38-7.32 (1H, d), 7.25-7.12 (2H, m), 4.1-3.9 (1H, s, br), 3.75-3.65 (2H, d), 3.3 (1H, m), 3.12-2.98 (2H, t), 2.1-1.9 (2H, m), 1.65-1.45 (2H, m), 1.3-1.2 (2H, d).

EXAMPLE 132

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]piperidin-4-yl}pyrimidin-2-amine

Prepared in a similar manner to Example 131 from Intermediate 2 (100 mg) and Intermediate 27 (83 mg). Purification by prep HPLC (Method A) afforded the title compound as a yellow solid (26 mg, 25%). LCMS 472/474 $[M+H]^+$, RT 2.91 min. ^1H NMR 300 MHz (d_6-DMSO) 11.95-11.8 (1H, s, br), 8.5-8.4 (1H, s, br), 8.25 (1H, s), 7.95-7.8 (2H, m), 7.55-7.45 (1H, d), 7.38-7.28 (1H, d), 7.28-7.18 (1H, t), 7.18-6.92 (1H, s, br), 3.82-3.78 (1H, s), 3.78-3.55 (2H, d), 2.75-2.55 (2H, t), 2.1-1.9 (2H, m), 1.7-1.5 (2H, m).

EXAMPLE 133

4-Imidazo[1,2-a]pyridin-3-yl-*N*-[1-(isopropylsulfonyl)piperidin-4-yl]pyrimidin-2-amine

To a suspension/solution of Example 121 (100 mg) in dry DCM/DMF (10 ml/5 ml) under nitrogen was added TEA (0.16 ml). Isopropylsulphonyl chloride (0.04 ml) was then added and the reaction mixture was stirred at r.t. overnight. LCMS showed a mixture of product and starting material. The solvent was removed in vacuo and the residues dissolved in dry DCM/DMF (10 ml/5 ml) under nitrogen and to this added DIPEA (0.2 ml) and isopropylsulphonyl chloride (0.04 ml). The reaction mixture was stirred for 3 days and the solvent was removed *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as an ivory cream solid (15.2 mg, 17%). LCMS (pH5.8) 401 $[M+H]^+$, RT 2.95 min. ^1H NMR 300 MHz (d_6-DMSO) 10.25-10.1 (1H, s, br), 8.55 (1H, s), 8.25 (1H, d), 7.8-7.7 (1H, d), 7.5-7.35 (2H, m), 7.25-7.05 (2H, d), 4.05-3.9 (1H, m), 3.75-3.6 (2H, d), 3.4-3.25 (1H, m), 3.2-3.0 (2H, m), 2.1-1.9 (2H, m), 1.65-1.4 (2H, m), 1.3-1.2 (6H, d).

EXAMPLE 134

4-Imidazo[1,2-a]pyridin-3-yl-*N*-[1-(methylsulfonyl)piperidin-4-yl]pyrimidin-2-amine

To a solution of Example 121 (75 mg) in dry DCM/DMF (10 ml/5 ml) under nitrogen was added methanesulfonyl chloride (0.02ml) and DIPEA (0.16 ml). The reaction mixture was stirred at r.t. overnight and the solvents removed *in vacuo*. Purification by column chromatography on reverse phase silica eluting with 0-100% (MeOH + 0.04% formic acid)/(H_2O + 0.04% formic acid) afforded the title compound as a yellow solid (17 mg, 24%). LCMS 373 $[M+H]^+$, RT 1.62 min. ^1H NMR 400 MHz (d_6-DMSO, 50°C) 10.1-10.0 (1H, s, br), 8.5 (1H, s), 8.3 (1H, s), 7.75 (1H, d), 7.55-7.45 (1H, t), 7.2-7.0 (2H, m), 4.0-3.9 (1H, m), 3.65-3.55 (2H, d), 3.0-2.9 (2H, m), 2.9 (3H, s), 2.1-2.0 (2H, d), 1.7-1.65 (2H, m).

EXAMPLE 135

4-Imidazo[1,2-a]pyridin-3-yl-*N*-{1-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]piperidin-4-yl}pyrimidin-2-amine

Prepared in a similar manner to Example 134 from Example 121 (75 mg) and 1-methylimidazole-4-sulphonyl chloride (37 mg). Purification by trituration in DMSO afforded the title compound as a white solid (62 mg, 76%). LCMS 439 $[M+H]^+$, RT 1.69 min. ^{1}H NMR 300 MHz (d_6-DMSO) 1.22-1.08 (1H, s, br), 8.55-8.5 (1H, s), 8.3-8.2 (1H, d), 7.95-7.8 (2H, m), 7.8-7.68 (1H, d), 7.55-7.45 (1H, t), 7.45-7.35 (1H, d), 7.2 (1H, d), 7.2-7.0 (1H, m), 3.85-3.7 (3H, s, br), 3.7-3.55 (2H, d), 2.8-2.6 (2H, m), 2.12-1.9 (2H, m), 1.7-1.48 (2H, m).

EXAMPLE 136

5-Chloro-4-imidazo[1,2-a]pyridin-3-yl-*N*-[1-(isopropylsulfonyl)piperidin-4-yl]pyrimidin-2-amine

To a solution of Example 126 (50 mg) in dry DCM/DMF (3 ml/3 ml) under nitrogen was added isopropylsulfonyl chloride (16 mg) and TEA (70 µl). The reaction mixture was stirred at r.t. overnight and partitioned between EtOAc (100 ml) and sodium hydrogencarbonate solution (50 ml). The organic layer was washed with brine (20 ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Trituration in EtOAc/Et_2O afforded the title compound as a yellow solid (50 mg, quantitative). LCMS 435/437 $[M+H]^+$, RT 2.49 min. ^{1}H NMR 300 MHz (d_6-DMSO) 8.78-8.6 (1H, s, br), 8.45 (1H, s), 7.8-7.4 (4H, m), 7.3-7.1 (1H, m), 4.05-3.85 (1H, m), 3.75-3.62 (2H, d), 3.45-3.2 (1H, m), 3.12-2.8 (1H, t), 2.05-1.9 (2H, t), 1.65-1.4 (3H, t), 1.12-1.0 (6H, m).

EXAMPLE 137

Ethyl (4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)(oxo)acetate

To a solution of the bis HCl salt of Example 32 (90 mg) in dry MeCN (5 ml) under nitrogen was added ethyl oxalyl chloride (0.025 ml) and TEA (0.14 ml). The mixture was stirred at r.t. for 2 days. More ethyl oxalyl chloride (0.03 ml) and DMF (1 ml) were added and the mixture heated in a microwave at 70°C for 10 min. More ethyl oxalyl chloride (0.03 ml) was added and the mixture stirred at r.t. overnight. The solvents were removed *in vacuo* and the residue was purified by prep HPLC (method A) to afford the title compound as beige solid (33.6 mg, 35%). LCMS 428/430 $[M+H]^+$, RT 3.38 min. ^{1}H NMR 300 MHz (d_6-DMSO) 8.7-8.5 (1H, s, br), 8.5 (1H, s), 8.3 (1H, s), 7.52-7.45 (1H, d), 7.4-7.3 (1H, d), 7.25-7.1 (2H, m), 4.35-4.25 (2H, m), 4.25-4.18 (1H, m), 4.18-4.0 (1H,

m), 3.65-3.55 (1H, d), 3.38-3.25 (1H, m), 3.08-2.9 (1H, t), 2.12-1.95 (2H, m), 1.6-1.35 (2H, m), 1.32-1.22 (3H, t).

EXAMPLE 138

Methyl (4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)(oxo)acetate

To a suspension of the bis TFA salt of Example 32 (500 mg) in dry DMF (15 ml) under nitrogen cooled to 0°C was added TEA (0.44 ml). To this solution was added dropwise a solution of methyl chlorooxoacetate (133 mg) in dry DMF (5 ml). The reaction mixture was allowed to warm to r.t. and stirred overnight. It was then cooled to 0°C and more chlorooxoacetate (110 mg) was added dropwise to the reaction mixture. The reaction was allowed to warm to r.t. and stirred for 2 hours. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (150 ml) and water (20 ml). The organic layer was washed with a saturated solution of brine (20 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by prep HPLC (method A) afforded the title compound as a cream solid (230 mg, 62%). LCMS 414/416 $[M+H]^+$, RT 3.18 min. ^1H NMR 300 MHz (d_6-DMSO) 11.92-11.82 (1H, s), 8.71-8.51 (1H, m), 8.5-8.45 (1H, d), 8.3 (1H, s), 7.51-7.45 (1H, d), 7.4-7.32 (1H, d), 7.25-7.1 (2H, m), 4.3-4.19 (1H, d), 4.19-4.05 (1H, m), 3.85 (3H, s), 3.69-3.55 (1H, d), 3.39-3.22 (1H, m), 3.1-2.9 (1H, t), 2.15-1.98 (2H, m), 1.6-1.38 (2H, m).

EXAMPLE 139

(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)(oxo)acetic acid hydrochloride

To a suspension of the bis TFA salt of Example 32 (500 mg) in dry DCM (40 ml) under nitrogen cooled to 0°C was added slowly TEA (0.44 ml) followed by methyl chlorooxoacetate (0.09 ml) dropwise. The reaction mixture was stirred at 0°C for 60 min. It was then allowed to warm to r.t. and stirred for 60 min. The reaction mixture was re-cooled to 0°C and more methyl chlorooxoacetate (0.042 ml) was added dropwise to the mixture. Stirring at 0°C was continued for 135 min. The reaction mixture was diluted with DCM (200 ml) and washed with water (50 ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting orange solid (600 mg) was suspended/dissolved in MeOH/water (10 ml/10 ml) and to this added NaOH (190 mg). The reaction mixture was heated at reflux for 3 hours. It was then allowed to cool and most of the MeOH was removed *in vacuo*. The residue was acidified to pH 2 resulting in a yellow precipitate. This was filtered off, washed with water, washed with

Et_2O and dried *in vacuo*. Trituration of the residue in MeOH/DCM (1:20) yielded the title compound as a yellow solid (260 mg, 66%). LCMS 400/402 $[M+H]^+$, RT 2.55 min. ^1H NMR 300 MHz (d_6-DMSO) 11.98-11.8 (1H, s, br), 8.7-8.5 (1H, m), 8.5-8.45 (1H, d), 8.3-8.22 (1H, s), 7.55-7.42 (1H, d), 7.4-7.3 (1H, d), 7.25-7.1 (2H, m), 4.29-4.15 (1H, d), 4.15-3.95 (1H, m), 3.7-3.55 (1H, d), 3.55-3.2 (1H, m, br), 3.05-2.85 (1H, m), 2.18-1.95 (2H, m), 1.6-1.33 (2H, m).

EXAMPLE 140

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methyl-2-oxoacetamide

To a solution of Example 139 (80 mg) in DMF (0.5 ml) and DCM (3 ml) was added HBTU (84 mg), DIPEA (0.07 ml) and methylamine hydrochloride (15 mg). The reaction mixture was stirred at r.t. overnight. The solvents were then removed *in vacuo* and the residue was purified by prep HPLC (Method A) to afford the title compound as beige solid (25 mg, 33%). LCMS 413/415 $[M+H]^+$, RT 2.65 min. ^1H NMR 300 MHz (d_6-DMSO) 11.9-11.8 (1H, s), 8.78-8.54 (2H, m), 8.5-8.45 (1H, d), 8.3 (1H, s), 7.53-7.45 (1H, d), 7.45-7.33 (1H, d), 7.3-7.13 (2H, m), 4.35-4.22 (1H, d), 4.2-4.0 (1H, m), 3.92-3.8 (1H, d), 3.28-3.12 (1H, t), 2.96-2.82 (1H, t), 2.7-2.6 (3H, d), 2.1-1.9 (2H, m), 1.6-1.45 (2H, m).

EXAMPLE 141

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*,*N*-dimethyl-2-oxoacetamide

Prepared in a similar manner to Example 143 from Example 139 (80 mg) and dimethylamine hydrochloride (18 mg). Purification by prep HPLC (Method A) afforded the title compound as yellow solid (21 mg, 27%). LCMS 427/429 $[M+H]^+$, RT 2.75 min. ^1H NMR 300 MHz (d_6-DMSO) 11.92-11.82 (1H, s, br), 8.7-8.52 (1H, m), 8.45 (1H, d), 8.35 (1H, s), 7.52-7.45 (1H, d), 7.38-7.32 (1H, d), 7.25-7.12 (2H, m), 4.32-4.25 (1H, d), 4.2-4.0 (1H, m), 3.58-3.47 (1H, d), 3.35-3.15 (2H, m), 2.97-2.87 (6H, d), 2.08-1.95 (2H, m), 1.61-1.49 (2H, m).

EXAMPLE 142

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(2-morpholin-4-ylethyl)piperidine-1-carboxamide

4-(*N*-BOC Amino) piperidine (100 mg) was dissolved in DCM (10 ml) and cooled to –78°C under nitrogen. TEA (0.2 ml) was added followed by triphosgene (52 mg) and the

mixture was stirred at 0°C for 30 min. 4-(2-Aminoethyl)morpholine (0.07ml) was added and the reaction was stirred at r.t. for 2 days. The reaction mixture was diluted with water (50 ml) and extracted with DCM (3 x 50 ml). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give a yellow solid. Trituration with Et_2O afforded a solid, which was dissolved in DCM (1 ml) and stirred with HCl (2.0M in Et_2O) (2 ml) at room temperature for 1 hour. The solvent was removed *in vacuo* to give a yellow solid. This was dissolved in DMF (5 ml) with stirring under nitrogen and Intermediate 2 (226 mg) was added followed by Na_2CO_3 (300 mg). The reaction mixture was heated at 100°C for 4 hours. The DMF was removed *in vacuo* and the resulting brown residue was dissolved in MeOH (10ml) at room temperature. KOH (141mg) was added and the reaction mixture stirred for 18 hours. The reaction mixture was filtered and solvent removed *in vacuo* to give a brown residue that was purified by prep HPLC (Method A) to give the title compound as a yellow solid (4.9 mg, 2%). LCMS 484/486 $[M+H]^+$ RT 1.92 min. ^1H NMR 300 MHz (d_4-MeOH) 8.60 (1H, d), 8.45 (1H, s), 8.15 (1H, s), 7.45 (1H, d), 7.20-7.10 (2H, m), 4.10-3.95 (3H, m), 3.80-3.70 (4H, m), 3.40-3.35 (2H, m), 3.05-2.95 (2H, m), 2.85-2.70 (6H, m), 2.15-2.05 (2H, m), 1.55-1.40 (2H, m).

EXAMPLE 143

Formic acid - 5-chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(4-methylpiperazin-1-yl)carbonyl]-piperidin-4-yl}pyrimidin-2-amine (1:1)

To a solution of Example 32 (50 mg) in DMF (10ml) under nitrogen was added 4-methyl-1-piperazine carbonyl chloride (36 mg) and TEA (53 µl) and the reaction stirred at r.t. for 2 days. The solvent was removed *in vacuo* and the residue purified by column chromatography on reverse phase silica eluting with 0-100% (MeOH + 0.04% formic acid)/(H_2O + 0.04% formic acid) to give a solid. This solid was further purified by prep. HPLC (Method A) to give the title compound as a pale yellow solid (27.4 mg, 39%). LCMS 454/456 $[M+H]^+$ (Free base) RT 1.92 min. ^1H NMR 300 MHz (d_4-MeOH) 8.65 (1H, d), 8.50 (1H, s), 8.35 (1H, s), 8.20 (1H, s), 7.50 (1H, d), 7.25-7.15 (2H, m), 4.15-4.05 (1H, m), 3.85-3.75 (2H, m), 3.50-3.40 (4H, m), 3.15-3.00 (6H, m), 2.70 (3H, s), 2.20-2.10 (2H, m), 1.70-1.50 (2H, m).

EXAMPLE 144

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(pyridin-2-ylmethyl)piperidine-1-carboxamide

2-(Aminomethyl)pyridine (29.8 mg) was dissolved in DCM (20ml) and cooled to 0°C in an ice bath. Triphosgene (25.2 mg) and TEA (100µl) were added and the reaction mixture allowed to warm to room temperature over 30 min. The bis HCl salt of Example 32 (100 mg) was added and the reaction mixture stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method B) to give the title compound as a light beige solid (13.3 mg, 11.5%). LCMS (pH 5.8) 462 $[M+H]^+$ RT 3.07 min. ^{1}H NMR 300 MHz (d_6-DMSO) 8.50 (2H, m), 8.30 (1H, s), 7.40-7.30 (1H, m), 7.55-7.45 (1H, m), 7.40-7.10 (5H, m), 4.35-4.30 (2H, d), 4.10-3.90 (3H, m), 2.95-2.80 (2H, m), 2.10-1.90 (2H, m), 1.60-1.40 (2H, m).

EXAMPLE 145

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(1,1-dioxidotetrahydro-3-thienyl)piperidine-1-carboxamide

Prepared in similar manner to Example 144 from the TFA salt of Example 32 (100 mg) and 1,1-dioxidotetrahydro-thien-3-ylamine hydrochloride (39 mg). Purification by prep HPLC (Method B) afforded the title compound as a white solid (7.9 mg, 8%). LCMS (pH 5.8) 489/491 $[M+H]^+$ RT 2.98 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.70-8.55 (1H, s, br), 8.50 (1H, s, br), 8.25 (1H, s), 7.50 (1H, d), 7.30-7.25 (1H, d), 7.20-7.10 (2H, m), 6.80 (1H, d), 4.40-4.30 (1H, m), 4.05-3.90 (3H, m), 3.40-3.25 (2H, m), 3.20-3.05 (1H, m), 2.95-2.80 (3H, m), 2.40-2.25 (1H, m), 2.15-2.00 (1H, m), 2.00-1.85 (2H, m), 1.50-1.30 (2H, m).

EXAMPLE 146

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-[2-(1,1-dioxidothiomorpholin-4-yl)ethyl]piperidine-1-carboxamide - 4-nitrophenol (1:1)

To a solution of thiomorpholine-4-(2-aminoethyl)-1,1-dioxide hydrochloride (43 mg) in dry DMF (3 ml) under nitrogen was added bis(4-nitrophenyl)carbonate (61 mg) and TEA (70 µl). The reaction mixture was stirred at room temperature for 2.5 hours, after which the bis HCl salt of Example 32 (80 mg) was added and the mixture heated to 100°C for 25 min in a microwave. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method B) to give the title compound as a white solid (3.5 mg, 3%). LCMS 532/534 $[M+H]^+$ RT 2.87 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.70-8.55 (1H, s, br), 8.50 (1H, s, br), 8.35-8.20 (3H, m), 7.60-7.45 (3H, m), 7.30-7.25 (1H, d), 7.20-7.10 (2H, m), 6.50 (1H, m), 4.10-3.80 (5H, m), 3.40-3.20 (4H, m), 3.15-3.05 (4H, m), 2.90-2.75 (4H, m), 2.00-1.80 (2H, m), 1.50-1.30 (2H, m).

EXAMPLE 147

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-piperidin-4-ylpiperidine-1-carboxamide

To a suspension of Example 32 (80 mg) in dry THF (12 ml) under nitrogen was added 4-isocyanato-1-trifluoroacetyl piperidine (60 mg) and the mixture stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue triturated with Et_2O to give a yellow solid (90 mg). A portion of this solid (75 mg) was dissolved in MeOH/water (4 ml/1 ml) and K_2CO_3 (38mg) was added. The reaction mixture was stirred at r.t. overnight. The mixture was diluted with water (10 ml) and extracted sequentially with DCM (50 ml), EtOAc (50 ml) and DCM (50 ml). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the title compound as a white solid (44 mg, 40%). LCMS 454/456 $[M+H]^+$ RT 1.91min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.70-8.55 (1H, s, br), 8.50 (1H, s), 8.25 (1H, s), 7.50 (2H, d), 7.30-7.10 (3H, m), 6.20 (1H, d), 4.10-3.85 (3H, m), 3.50-3.30 (1H, m), 2.95-2.85 (2H, m), 2.85-2.65 (2H, m), 2.50-2.35 (2H, m), 2.00-1.80 (2H, m), 1.45-1.20 (4H, m).

EXAMPLE 148

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-piperidin-3-ylpiperidine-1-carboxamide

Prepared in similar manner to Example 147 from Example 32 (80mg) and 3-isocyanato-1-trifluoroacetyl piperidine (60mg) to give the title compound as a white solid (52 mg, 47%). LCMS 454/456 $[M+H]^+$ RT 1.93mins. ^1H NMR 300 MHz (d_6-DMSO) 11.80 (1H, s, br), 8.65-8.50 (1H, s, br), 8.45 (1H, s), 8.20 (1H, s), 7.45 (2H, d), 7.25-7.05 (3H, m), 6.15 (1H, d), 4.05-3.80 (3H, m), 3.45-3.30 (1H, m), 2.85-2.65 (3H, m), 2.35-2.15 (3H, m), 1.95-1.80 (2H, m), 1.75-1.65 (1H, m), 1.55-1.45 (1H, m), 1.40-1.20 (4H, m).

EXAMPLE 149

Formic acid - *N*-ethyl-4-{[4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxamide (1:1)

To a solution of Example 21 (82 mg) in MeOH (10ml) was added NaOH (10mg) followed by palladium on carbon (50 mg). The reaction mixture was stirred under an atmosphere of hydrogen for 3 hours, after which the solution was neutralised with 1M HCl and filtered through a pad of celite. The solvent was removed *in vacuo* to give a yellow gum, which was purified by column chromatography on reverse phase silica eluting with 0-100% (MeOH + 0.04% formic acid)/(H_2O with 0.04% formic acid) to give

the title compound as a yellow solid (44 mg, 59%). LCMS 365 $[M+H]^+$ (Free base) RT 1.83 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.50-8.45 (1H, m), 8.20 (1H, s), 8.10 (1H, s), 7.95 (1H, d), 7.45-7.40 (1H, m), 7.20-7.15 (2H, m), 7.05 (1H, d), 4.15-3.95 (3H, m), 3.20-3.10 (2H, q), 3.05-2.90 (2H, m), 2.15-2.05 (2H, m), 1.55-1.40 (2H, m), 1.15-1.05 (3H, t).

EXAMPLE 150

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(morpholin-4-ylacetyl)piperidin-4-yl]pyrimidin-2-amine

To a solution of Example 32 (100 mg) in MeCN (10 ml) at r.t. under nitrogen was added chloroacetyl chloride (24.3 ul) and TEA (43ul) and stirring continued for 1.5 hours. Morpholine (87 ul) was added and stirring continued for 18 hours. The solvents were evaporated *in vacuo* and the residue purified by prep HPLC (Method A) to give the title compound as an off-white solid (35 mg, 25%). LCMS 455/457 $[M+H]^+$, RT 1.94 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.6 (1H, s, br), 8.5 (1H, d), 8.3 (1H, s), 7.55-7.10 (4H, m), 4.40-4.30 (1H, m), 4.20-4.00 (2H, m), 3.75-3.50 (2H, m), 3.45-2.95 (4H, m), 2.90-2.70 (2H, m), 2.60-2.30 (4H, m), 2.15-1.90 (2H, m), 1.60-1.30 (2H, m).

EXAMPLE 151

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(4-methylpiperazin-1-yl)acetyl]piperidin-4-yl}pyrimidin-2-amine hydrochloride

Prepared in similar manner to Example 150 from Example 32 (40 mg) and *N*-methylpiperazine (55 µl) to give the title compound as an off-white solid (12.8 mg, 22%). HCl was added to the test sample to aid solubility in DMSO. LCMS 468/470 $[M+H]^+$ (Free base), RT 1.91 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.6 (1H, s, br), 8.5 (1H, d), 8.3 (1H, s), 7.55-7.10 (4H, m), 4.40-4.30 (1H, m), 4.20-4.00 (2H, m), 3.40-1.25 (19H, m).

EXAMPLE 152

Formic acid - 5-chloro-*N*-{1-[(dimethylamino)acetyl]piperidin-4-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine (1:1)

Prepared in similar manner to Example 150 from Example 32 (40 mg) and dimethylamine hydrochloride (41 mg) to give the title compound as a pale yellow solid (18.1 mg, 32%). LCMS 413/415 $[M+H]^+$ (Free base), RT 1.94 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.6 (1H, s, br), 8.5 (1H, s, br), 8.25 (1H, s), 8.20 (1H, s), 7.55-7.10 (4H, m), 4.40-4.30 (1H, m), 4.15-4.00 (2H, m), 3.20-3.00 (2H, m) 2.85-2.65 (2H, m), 2.55 (3H, s), 2.20 (3H, s), 2.10-1.90 (2H, m), 1.60-1.30 (2H, m).

EXAMPLE 153

Formic acid - *N*-[1-(aminoacetyl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine (1:1)

Prepared in similar manner to Example 150 from Example 32 (40 mg) and aqueous ammonia (19 μl) to give the title compound as a glass (10 mg, 16%). LCMS 385/387 $[M+H]^+$ (Free base), RT 1.86 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.65 (1H, d), 8.5 (1H, s), 8.45 (1H, br s), 8.20 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 4.55-4.45 (1H, m), 4.25-4.10 (1H, m), 4.00 (2H, d), 3.85-3.75 (1H, m), 3.35-3.00 (2H, m) 2.30-2.10 (2H, m), 1.75-1.50 (2H, m).

EXAMPLE 154

Formic acid - 5-chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(methylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine (1:1)

Prepared in similar manner to Example 150 from Example 32 (40 mg) and methylamine (2M in THF) (0.25 ml) to give the title compound as a glass (3.9 mg, 6%). LCMS 399/401 $[M+H]^+$ (Free base), RT 1.93 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.65 (1H, d), 8.5 (1H, br s), 8.45 (1H, s), 8.20 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 4.55-4.45 (1H, m), 4.25-4.15 (1H, m), 4.10 (2H, d), 3.85-3.75 (1H, m), 3.40-3.25 (1H, m), 3.10-3.00 (1H, m), 2.75 (3H, s), 2.30-2.10 (2H, m), 1.75-1.50 (2H, m).

EXAMPLE 155

Formic acid - 5-chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(pyridin-3-ylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine (1:1)

Prepared in similar manner to Example 150 from Example 32 (40 mg) and 3-aminopyridine (47 mg) to give the title compound as a beige solid (26.1 mg, 36%). LCMS 462/464 $[M+H]^+$ (Free base), RT 1.99 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.65 (1H, d), 8.5 (1H, s), 8.35 (1H, s), 8.20 (1H, s), 8.00-7.90 (2H, m), 7.75-7.65 (2H, m), 7.50 (1H, d), 7.30-7.15 (2H, m), 5.65-5.50 (2H, m), 4.55-4.45 (1H, m), 4.30-4.15 (1H, m), 4.00-3.85 (1H, m), 3.50-3.35 (1H, m), 3.15-3.00 (1H, m) 2.40-2.10 (2H, m), 1.85-1.50 (2H, m).

EXAMPLE 156

3-(2-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-oxo-ethyl)-1,1-dimethyl-urea

To a solution of the bis HCl salt of Example 32 (50 mg) in MeCN (10 ml) at room temperature under nitrogen was added chloroacetyl chloride (10 μl) and TEA (53 μl). The mixture was stirred at r.t. for 16 hours. Excess 0.88M aqueous NH_3 (~1 ml) was then

added and the reaction stirred for 72 hours. HPLC analysis showed incomplete conversion so the reaction mixture was heated in a microwave reactor at 90°C for 10mins. The solvents were removed *in vacuo* and the residue was combined with DCM (10 ml), TEA (~1 ml) and dimethyl carbamyl chloride (21 µl). The reaction mixture was stirred at r.t. for 16 hours, concentrated *in vacuo* and purified by column chromatography on silica eluting with MeOH/DCM to give the title compound as an off-white solid (17.7 mg, 31%). LCMS 456/458 $[M+H]^+$, RT 2.54 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.6 (1H, s, br), 8.5 (1H, d), 8.25 (1H, s), 7.55-7.10 (4H, m), 6.30 (1H,t), 4.40-4.30 (1H, m), 4.15-3.80 (4H, m), 3.20-3.00 (2H, m) 2.80 (6H, s), 2.10-1.90 (2H, m), 1.60-1.30 (2H, m).

EXAMPLE 157

Morpholine-4-carboxylic acid (2-{4-[5-chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-oxo-ethyl)-amide

Prepared in similar manner to Example 156 from the bis HCl salt of Example 32 (80 mg) and morpholine carbonyl chloride (50 µl). Purification by column chromatography on silica eluting with 0-100% MeOH/DCM followed by prep HPLC (Method A) afforded the title compound as a brown solid (5.5 mg, 6%). LCMS 498/500 $[M+H]^+$, RT 2.54 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.65 (1H, m), 8.45 (1H, s), 8.20 (1H, s), 7.45 (1H, d), 7.25-7.15 (2H, m), 4.55-4.45 (1H, m), 4.25-3.90 (4H, m), 3.65 (4H, t), 3.40 (4H, t), 3.35-3.20 (1H, m), 3.00-2.90 (1H, m), 2.25-2.10 (2H, m), 1.65-1.45 (2H, m).

EXAMPLE 158

5-Chloro-*N*-[1-(1*H*-imidazol-1-ylacetyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

To the bis HCl salt of Example 32 (40 mg) in MeCN (5 ml) at r.t. under nitrogen was added TEA (140µl) and chloroacetyl chloride (10 µl). The reaction mixture was heated in microwave reactor at 100°C for 20 min. HPLC analysis showed incomplete conversion. DMF (1 ml) and more chloroacetyl chloride (20 µl) were added and the mixture was again heated in a microwave reactor at 100°C for 20 min. Imidazole (20 mg) was added and the reaction mixture was heated in a microwave reactor at 100°C for 10 min. HPLC analysis showed incomplete consumption of intermediate so more imidazole (50 mg) was added and the mixture heated in a microwave reactor at 100°C for 10 min. The reaction mixture was concentrated *in vacuo* and the residue purified by prep HPLC

(Method B) to give the title compound as an off-white solid (2.7 mg, 6%). LCMS (pH 5.8) 436/438 $[M+H]^+$, RT 2.84 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.60 (1H, s, br), 8.50 (1H, s), 8.25 (1H, s), 7.55-7.45 (2H, m), 7.40 (1H, d), 7.25 (2H, m), 7.05 (1H, s), 6.85 (1H, s), 5.15-4.95 (2H, m), 4.40-4.25 (1H, m), 4.15-3.85 (2H, m), 3.40-3.15 (1H, m), 3.00-2.80 (1H, m), 2.15-1.90 (2H, m), 1.60-1.35 (2H, m).

EXAMPLE 159

N-{(3*R*)-1-[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]pyrrolidin-3-yl}acetamide

To a solution of the bis HCl salt of Example 32 (30 mg) in DMF (3ml) at r.t. under nitrogen was added TEA (70 µl), and chloroacetyl chloride (6 µl). The mixture was stirred at r.t. for 2 hours. (3*R*)-(+)-3-acetamidopyrrolidine was added and the reaction mixture heated in a microwave reactor at 100°C for 5 mins. The solvent was removed *in vacuo* and the residue was purified by prep HPLC (Method B) to give the title compound (18.5 mg, 50%) as a tan solid. LCMS (pH 5.8) 496/498 $[M+H]^+$, RT 2.58 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.65 (1H, s, br), 8.50 (1H, s), 8.25 (1H, s), 8.00 (1H, d), 7.55-7.45 (2H, d), 7.35-7.25 (1H, m), 7.25-7.10 (2H, m), 4.40-4.25 (1H, m), 4.20-3.95 (3H, m), 3.45-3.25 (2H, m), 3.25-3.05 (2H, m), 2.80-2.70 (2H, m), 2.70-2.60 (1H, m), 2.40-2.30 (1H, m), 2.10-1.90 (3H, m), 1.75 (3H, s), 1.60-1.30 (3H, m).

EXAMPLES 160-198

Examples 160-198 were prepared using parallel synthesis techniques as described below. The bis HCl salt of Example 32 (3.6 g) was dissolved in DMF (117 ml). TEA (7 ml) and chloroacetyl chloride (0.715 ml) were then added and the reaction mixture was stirred at r.t. under nitrogen for 2.5 hours. The reaction mixture was then dispensed (1 ml per tube) into 118 tubes, which had been pre-prepared with the appropriate amines (1 mmol per tube). The tubes were shaken for 72 hours. LCMS analysis of four tubes at random showed that some conversions were incomplete. A solution of DMF/TEA (100 ml/18 ml) was then dispensed (1 ml per tube) across all tubes to aid solubility. Shaking was continued for another 24 hours. The solvents were removed *in vacuo* and DMSO (500 µl) added to each well. The desired products from each well were isolated by prep HPLC to yield on average 1 mg of the title compounds.

EXAMPLE 160

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(4-hydroxy-cyclohexylamino)-ethanone

LCMS 483/485 $[M+H]^+$, RT 1.9 min.

EXAMPLE 161

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-[cyclohexyl-(2-hydroxy-ethyl)-amino]-ethanone

LCMS 511/513 $[M+H]^+$, RT 2.3 min.

EXAMPLE 162

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-propylamino)-ethanone

LCMS 443/445 $[M+H]^+$, RT 1.9 min.

EXAMPLE 163

{1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidin-3-yl}methanol

LCMS 483/485 $[M+H]^+$, RT 2.0 min.

EXAMPLE 164

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(1-hydroxymethyl-cyclopentylamino)-ethanone

LCMS 483/485 $[M+H]^+$, RT 2.1 min.

EXAMPLE 165

1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]pyrrolidin-3-ol

LCMS 455/457 $[M+H]^+$, RT 1.9 min.

EXAMPLE 166

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(4-hydroxy-butylamino)-ethanone

LCMS 457/459 $[M+H]^+$, RT 1.9 min.

EXAMPLE 167

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-1-methyl-ethylamino)-ethanone

LCMS 443/445 $[M+H]^+$, RT 1.9 min.

EXAMPLE 168

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(1-hydroxymethyl-3-methyl-butylamino)-ethanone

LCMS 485/487 $[M+H]^+$, RT 2.2 min.

EXAMPLE 169

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(1-hydroxymethyl-propylamino)-ethanone

LCMS 457/459 $[M+H]^+$, RT 2.0 min.

EXAMPLE 170

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-1,1-dimethyl-ethylamino)-ethanone

LCMS 4557/459 $[M+H]^+$, RT 2.0 min.

EXAMPLE 171

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(1-hydroxymethyl-2-methyl-propylamino)-ethanone

LCMS 471/473 $[M+H]^+$, RT 2.1 min.

EXAMPLE 172

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-1-phenyl-ethylamino)-ethanone

LCMS 505/507 $[M+H]^+$, RT 2.2 min.

EXAMPLE 173

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-ethylamino)-ethanone

LCMS 429/431 $[M+H]^+$, RT 1.9 min.

EXAMPLE 174

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-[(1-hydroxy-cyclohexylmethyl)-amino]-ethanone

LCMS 497/499 $[M+H]^+$, RT 2.2 min.

EXAMPLE 175

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(3-hydroxy-propylamino)-ethanone

LCMS 443/445 $[M+H]^+$, RT 1.9 min.

EXAMPLE 176

2-{1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidin-2-yl}ethanol

LCMS 497/499 $[M+H]^+$, RT 2.1 min.

EXAMPLE 177

2-{1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidin-4-yl}ethanol

LCMS 497/499 $[M+H]^+$, RT 2.0 min.

EXAMPLE 178

1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidin-4-ol

LCMS 469/471 $[M+H]^+$, RT 1.9 min.

EXAMPLE 179

1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidine-4-carboxamide

LCMS 496/498 $[M+H]^+$, RT 1.9 min.

EXAMPLE 180

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-butylamino)-ethanone

LCMS 457/459 $[M+H]^+$, RT 2.0 min.

EXAMPLE 181

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(3-hydroxy-2,2-dimethyl-propylamino)-ethanone

LCMS 471/473 $[M+H]^+$, RT 2.1 min.

EXAMPLE 182

{(2*S*)-1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]pyrrolidin-2-yl}methanol

LCMS 469/471 $[M+H]^+$, RT 1.9 min.

EXAMPLE 183

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-1-methyl-ethylamino)-ethanone

LCMS 443/445 $[M+H]^+$, RT 1.9 min.

EXAMPLE 184

(3*R*)-1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidin-3-ol

LCMS 469/471 $[M+H]^+$, RT 1.9 min.

EXAMPLE 185

1-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-(2-hydroxy-propylamino)-ethanone

LCMS 443/445 $[M+H]^+$, RT 1.9 min.

EXAMPLE 186

(3*R*)-1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]pyrrolidin-3-ol

LCMS 455/457 $[M+H]^+$, RT 1.9 min.

EXAMPLE 187

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-({[2-(1*H*-indol-3-yl)ethyl]amino}acetyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 528/530 $[M+H]^+$, RT 2.4 min.

EXAMPLE 188

5-Chloro-*N*-(1-{[(1,3-dimethylbutyl)amino]acetyl}piperidin-4-yl)-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 469/471 $[M+H]^+$, RT 2.2 min.

EXAMPLE 189

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(pyrimidin-4-ylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 463/465 $[M+H]^+$, RT 2.0 min.

EXAMPLE 190

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(pyrrolidin-1-ylacetyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 439/441 $[M+H]^+$, RT 2.0 min.

EXAMPLE 191

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-{[(2-morpholin-4-ylethyl)amino]acetyl}piperidin-4-yl)pyrimidin-2-amine

LCMS 498/500 $[M+H]^+$, RT 1.8 min.

EXAMPLE 192

1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]-*N*,*N*-diethylpiperidine-3-carboxamide

LCMS 552/554 $[M+H]^+$, RT 2.3 min.

EXAMPLE 193

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-{[(2-methyl-2-morpholin-4-ylpropyl)amino]acetyl}-piperidin-4-yl)pyrimidin-2-amine

LCMS 526/528 $[M+H]^+$, RT 2.1 min.

EXAMPLE 194

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-({methyl[(1-methyl-1*H*-imidazol-2-yl)methyl]amino}-acetyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 493/495 $[M+H]^+$, RT 2.1 min.

EXAMPLE 195

3-(2-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-oxo-ethylamino)-benzenesulfonamide

LCMS 540/542 $[M+H]^+$, RT 3.0 min.

EXAMPLE 196

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-{[(2-pyrrolidin-1-ylethyl)amino]acetyl}piperidin-4-yl)pyrimidin-2-amine

LCMS 482/484 $[M+H]^+$, RT 1.6 min.

EXAMPLE 197

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}acetyl)-piperidin-4-yl]pyrimidin-2-amine

LCMS 496/498 $[M+H]^+$, RT 1.6 min.

EXAMPLE 198

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(1,3-thiazol-2-ylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 468/470 $[M+H]^+$, RT 2.0 min.

EXAMPLE 199

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[2-(methylamino)propanoyl]piperidin-4-yl}pyrimidin-2-amine

Prepared in similar manner to Example 150 from Example 32 (50 mg), 2-chloroproionyly chloride (14 µl) and methylamine (2M in THF) (0.3 ml). Purification by prep HPLC (Method A) afforded the title compound as a white solid (26.1 mg, 41%). LCMS 413/415 $[M+H]^+$, RT 1.96 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.65 (1H, d), 8.55 (1H, s, br), 8.50 (1H, s), 8.20 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 4.60-4.45 (1H, m),

4.45-4.35 (1H, m), 4.30-4.15 (1H, m), 4.00-3.85 (1H, m), 3.45-3.30 (1H, m), 3.15-2.95 (1H, m) 2.35-2.10 (2H, m), 1.75-1.40 (5H, m).

EXAMPLE 200

Formic acid - 5-chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(methylamino)(phenyl)acetyl]piperidin-4-yl}pyrimidin-2-amine (1:1)

Prepared in similar manner to Example 150 from Example 32 (100 mg) and 2-chloro-2-phenyl-acetyl chloride (48 µl) and methylamine (2M in THF) (0.6 ml) Purification by prep HPLC (Method A) afforded the title compound as a yellow solid (12.6mg, 8%). LCMS 475/477 $[M+H]^+$, RT 2.19 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.60-8.40 (2H, m), 8.20-8.1 (1H, m), 7.70-7.00 (8H, m), 5.50-5.30 (1H, m), 4.70-4.40 (1H, m), 4.20-4.00 (1H, m), 3.90-3.75 (1H, m), 3.40-2.80 (2H, m), 2.70-2.50 (3H, m), 2.20-2.05 (1H, m) 2.00-1.80 (1H, m), 1.70-1.55 (1H, m), 1.45-1.20 (1H, m).

EXAMPLE 201

(2-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-oxo-ethyl)-methyl-carbamic acid *tert*-butyl ester

To a suspension of Example 32 (400 mg), (*tert*-butoxycarbonyl-methyl-amino)-acetic acid (CAS 13734-36-6) (208 mg) and HATU (418 mg) in DMF (10 ml) was added DIPEA (0.871 ml). The resulting solution was stirred overnight at r.t.. The reaction mixture was concentrated *in vacuo* and redissolved in DCM (50 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (3 x 20 ml), washed with brine (20 ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 2-3% MeOH/DCM to give the title compound as a white solid (344 mg, 69%). LCMS 521/523 $[M+Na]^+$, RT 3.57 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.90 (1H, s), 8.60 (1H, s), 8.50 (1H, s), 8.30 (1H, s), 7.50-7.10 (4H, m), 4.40-4.30 (1H, m), 4.20-3.75 (3H, m), 3.20-3.05 (1H, m), 2.85-2.70 (4H, m), 2.10-1.90 (2H, m), 1.60-1.30 (11H, m).

EXAMPLE 202

N-(2-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-oxo-ethyl)-*N*-methyl-acetamide

To a solution of Example 154 (100 mg) and DIPEA (0.219 ml) in DCM (5 ml) cooled to 0°C was added acetyl chloride (0.015 ml). The reaction mixture was allowed to warm to r.t. and stirred overnight. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (3 x 5 ml), washed with brine (5 ml), separated, dried over $MgSO_4$,

filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 2-6% MeOH/DCM to give the title compound as a white solid (78 mg, 71%). LCMS 441/443 $[M+H]^+$, RT 2.59 min. ^{1}H NMR 300 MHz ($CDCl_3$) 11.50 (1H, s, br), 8.70 (1H, d), 8.20 (2H, s, br), 7.60 (1H, d), 7.25 (2H, m, 6.80 (1H, s, br), 4.90 (1H, d, br), 4.25 (1H, d, br), 3.7-3.2 (3H, m), 3.10 (3H, s), 2.70 (1H, m, br), 2.30 (4H, s, br), 1.7-1.2 (4H, m, br).

EXAMPLE 203

Tetrahydro-pyran-4-carboxylic acid (2-{4-[5-chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-oxo-ethyl)-amide

To a solution of tetrahydro-2*H*-pyran-4-carbonyl chloride (CAS 40191-32-0) (223 mg) in dry DCM (20 ml) was added glycine methyl ester HCl (207 mg) and TEA (0.42 ml). The reaction mixture was stirred at room temperature overnight. The mixture was washed with H_2O (2 x 20 ml) and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in THF (2 ml) and to this added 1M NaOH solution (10 ml). The reaction mixture was stirred at r.t. for 3 hours and the THF removed *in vacuo*. The aqueous layer was acidified to pH 5 using 1M HCl solution and extracted with EtOAc (2 x 40 ml). The organic layers were combined, dried over MgSO4, filtered and concentrated *in vacuo* to give an off-white solid. This was suspended in dry DCM (15 ml) under nitrogen along with Example 32 (54 mg) and to this mixture was added EDC.HCl (54 mg), HOBt (4 mg) and TEA (0.06 ml). The reaction mixture was stirred at room temperature for 16 hours before water (20 ml) was added. The organic layer was separated and the aqueous layer was extracted with DCM (20 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 0-10% MeOH/DCM to give the title compound as a yellow solid (16 mg, 2%). LCMS 497/499 $[M+H]^+$, RT 2.63 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.35 (1H, s), 8.60 (1H, s, br), 8.50 (1H, s), 8.25 (1H, s), 7.90 (1H, t), 7.50 (1H, d), 7.35 (1H, d), 7.25-7.10 (2H, m), 4.30 (1H, d), 4.2-3.8 (6H, m), 3.4-3.2 (2H, m), 3.15 (1H, m), 2.9-2.7 (1H, m), 2.5 (1H, m), 2.1-1.9 (1H, m), 1.6-1.3 (6H, m).

EXAMPLE 204

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(1,2,4-oxadiazol-3-ylmethyl)piperidin-4-yl]pyrimidin-2-amine

To a solution of Example 32 (114 mg) and 3-(chloromethyl)-1,2,4-oxadiazole (44 mg) in dry DMF (3 ml) was added Na_2CO_3 (51 mg). This mixture was stirred at 85°C for 2 hours and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 0-5% MeOH/DCM to give the title compound as a white solid (25 mg). LCMS 410/412 $[M+H]^+$, RT 1.96 min. ^1H NMR 300 MHz (d_6-DMSO) 12.35 (1H, s), 9.60 (1H, s), 8.60 (1H, s, br), 8.50 (1H, s), 8.20 (1H, s), 7.50 (1H, d), 7.30-7.05 (3H, m), 3.75 (3H, s, br), 2.90 (2H, d), 2.34-2.15 (2H, m), 2.05-1.70 (2H, m), 1.65-1.40 (2H, m).

EXAMPLE 205

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(pyridin-3-ylmethyl)piperidin-4-yl]pyrimidin-2-amine

To a solution of Example 32 (50 mg) and 3-picolyl chloride HCl (30 mg) in DMF (10 ml) was added Na_2CO_3 (32 mg). The reaction was stirred at 95°C for 3 hours and the solvent removed *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as a white solid (26 mg, 41%). LCMS (pH 5.8) 419/421 $[M+H]^+$, RT 3.14 min. ^1H NMR 300 MHz (CD_3OD) 8.65 (1H, d), 8.60 (1H, d), 8.50 (2H, m), 8.20 (1H, s), 7.90 (1H, d), 7.5-7.4 (2H, m), 7.3-7.1 (2H, m), 4.0-3.9 (1H, m), 3.70 (2H, s), 3.0-2.9 (2H, m), 2.4-2.25 (2H, m), 2.2-2.1 (2H, m), 1.8-1.6 (2H, m).

EXAMPLE 206

Formic acid - 5-chloro-4-(1*H*-indol-3-yl)-*N*-[1-(pyridin-2-ylmethyl)piperidin-4-yl]pyrimidin-2-amine (1:1)

To a solution of Intermediate 2 (200 mg) and Intermediate 28 (135 mg) in DMF (3 ml) was added Na_2CO_3 (173 mg). The reaction was stirred at 95°C for 5 hours and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (20 ml) and washed with water (20 ml). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude brown oil was dissolved in MeOH (94 ml) and KOH (38 mg) was added and the mixture stirred for 5 hours. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to give the title compound as a yellow solid (31 mg, 14%). LCMS 419 $[M+H]^+$ (Free base) RT 2.02 min. ^1H NMR 300 MHz ($CDCl_3$) 8.75 (1H, s, br), 8.6 (3H, m), 8.40 (1H, s), 8.20 (1H, s), 7.65 (1H, dt), 7.5-7.4 (2H, m), 7.35-7.25 (4H, m), 7.15 (1H, m), 5.05 (1H, d), 4.0 (1H, s, br), 3.70, (2H, s), 3.0-2.9 (2H, m), 2.4-2.25 (2H, t), 2.2-2.1 (2H, m), 1.8-1.6 (2H, m).

EXAMPLE 207

Formic acid - 5-chloro-4-(1*H*-indol-3-yl)-*N*-[1-(pyridin-4-ylmethyl)piperidin-4-yl]pyrimidin-2-amine (1:1)

Prepared in similar manner to Example 206 from Intermediate 2 (200 mg) and Intermediate 29 (135 mg). Purification by prep HPLC (Method A) afforded the title compound as a yellow solid (31 mg, 17%). LCMS 419 $[M+H]^+$ (Free base), RT 1.83 min. ^1H NMR 300 MHz ($CDCl_3$) 8.80 (1H, s, br), 8.1-8.0 (3H, m), 8.40 (1H, s), 8.25 (1H, s), 8.20 (1H, s), 7.5-7.4 (1H, d), 7.35-7.20 (5H, m), 5.40 (1H, s, br), 4.0 (1H, m), 3.60 (2H, s), 2.9 (2H, m), 2.40-2.25 (2H, m), 2.25-2.10 (2H, m), 1.80-1.60 (2H, m).

EXAMPLE 208

Formic acid - 5-chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(5-methylisoxazol-3-yl)methyl]piperidin-4-yl}pyrimidin-2-amine (1:1)

A mixture of 4-(BOC-amino)piperidine (500 mg), 3-(chloromethyl)-5-methylisoxazole (394 mg) and Na_2CO_3 (265 mg) in dry DMF (15 ml) under nitrogen was heated to 95°C overnight. The DMF was removed *in vacuo* and the residue partitioned between EtOAc (150 ml) and water (50 ml). The organic layer was separated, dried over $MgSO_4$, filtered and the concentrated *in vacuo* to give a brown oil. Purification by column chromatography on silica eluting with 30-100% EtOAc/heptane afforded a brown solid. This was dissolved in dry MeOH (1 ml) and to it added a solution of HCl (2M in Et_2O) (6 ml). The mixture was stirred at r.t. overnight. The resulting solid was filtered off, washed with Et_2O and dried *in vacuo* to yield the intermediate amine as a beige solid (537 mg). To a solution of this solid (75 mg) and Intermediate 2 (100 mg) in DMF (20 ml) was

added Na_2CO_3 (84 mg). The reaction was stirred at 90°C for 1 hour. More intermediate amine (75 mg) was added and heating at 90°C was continued for 2 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography eluting with 50-100% EtOAc/heptane. The resulting product was dissolved in MeOH (10 ml), KOH (8.5 mg) added and the mixture stirred at r.t. for 1 hour. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (100 ml). The organic layer was washed with water (30 ml), separated, filtered, and concentrated *in vacuo*. Purification by prep HPLC (Method A) afforded the title compound as an off-white solid (12.4 mg, 9%). LCMS 423/425 $[M+H]^+$ (Free base) RT 2.01 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.50 1H, d), 8.35 (1H, s), 8.20 (1H, s), 8.05 (1H, s), 7.35 (1H, d), 7.20-7.00 (2H, m), 6.10 (1H, s), 3.90 (1H, s, br), 3.70 (1H, s), 3.05 (2H, m), 2.50-2.40 (2H, m), 2.30 (3H, s), 2.10-2.00 (2H, m), 1.70-1.50 (2H, m)

EXAMPLE 209

1-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)acetone

To a solution of Example 32 (154 mg) and ethyl 2-chloroacetoacetate (0.019 ml) in MeCN (5 ml) was added TEA (0.14 ml). The mixture was heated with microwaves in a sealed tube at 100°C for 10 min. Added to this mixture was DMF (1 ml) and more ethyl 2-chloroacetoacetate (0.040 ml) and this mixture was heated at100°C for 10 min. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method A) to give the title compound as a tan solid (2.9 mg, 2%). LCMS 384/386 $[M+H]^+$, RT 1.85 min. ^{1}H NMR 300 MHz (CD_3OD) 8.60 (1H, d), 8.45 (1H, d), 8.20 (1H, s), 7.45 (1H, d), 7.30-7.15, (2H, m), 4.05 (1H, m), 3.75 (2H, s), 3.20 (2H, m), 2.70 (2H, m), 2.25 (2H, m), 2.20 (3H, s), 1.90-1.75 (2H, m).

EXAMPLE 210

Methyl (4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)acetate

Prepared in similar manner to Example 204 from the bis HCl salt of Example 32 (100 mg) and methyl bromoacetate (0.024 ml). Removal of the solvent *in vacuo* afforded the title compound as an off-white solid (11.3 mg, 11%). LCMS 400/402 $[M+H]^+$, RT 1.94 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.65 (1H, d), 8.50 (1H, s), 8.15 (1H, s), 7.45 (1H, d), 7.30-7.15 (2H, m), 3.95 (1H, m), 3.75 (3H, s), 3.10-3.00 (2H, m), 2.50-2.35 (2H, m), 2.20-2.05 (2H, m), 1.80-1.60 (2H, m).

EXAMPLE 211

(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)acetic acid bis(trifluoroacetate)

To a solution of Example 32 (460 mg) and *tert*-butyl bromoacetate (0.25 ml) in DMF (20 ml) was added Na_2CO_3 (164 mg). The reaction was stirred at r.t. overnight and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (100 ml) and washed with water (50 ml). The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica eluting with 50-100% EtOAc/heptane. The resulting ester was dissolved in DCM (10 ml) and TFA (1.3 ml) added. The reaction mixture was stirred at r.t overnight and the solvents removed *in vacuo* to give the title compound as a yellow powder (228 mg, 26%). LCMS 386/388 $[M+H]^+$ (Free base) RT 2.05 min. ^1H NMR 300 MHz (d_6-DMSO at 90°C) 11.55 (1H, s, br), 8.55 (1H, d), 8.40 (1H, d), 8.30 (1H, s), 7.50 (1H, m), 7.25-7.15 (2H, m), 4.10 (1H, s, br), 4.05 (1H, s), 3.55 (2H, m), 3.25 (2H, m), 2.20 (2H, m), 2.00 (2H, m).

EXAMPLES 212-223

Examples 212-223 were prepared using parallel synthesis techniques as described below. A stock solution of Example 211 (0.5 M in NMP) (200 µl) was dispensed into each of the used wells of a Whatman 48 deep well plate. Solutions of the appropriate amines (0.5 M in NMP) (200 µl) were added to the individual wells. A solution of EDC.HCl (0.2 M in DCM) (500 µl) and a solution of HOBt (0.2 M in NMP) (50 µl) were added to each well and the plate shaken for 18 hours. The solvents were removed *in vacuo* and DMSO (500 µl) added to each well. The desired products from each well were isolated by prep HPLC (Method A) to yield on average 1 mg of the title compounds.

EXAMPLE 212

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-(2-fluorophenyl)acetamide

LCMS 479/481 $[M+H]^+$, RT 2.3 min.

EXAMPLE 213

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-[2-(1*H*-indol-3-yl)ethyl]acetamide

LCMS 528/530 $[M+H]^+$, RT 2.3 min.

EXAMPLE 214

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-pyrimidin-4-ylacetamide

LCMS 463/465 $[M+H]^+$, RT 1.9 min.

EXAMPLE 215

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-pyridin-3-ylacetamide

LCMS 462/464 $[M+H]^+$, RT 1.8 min.

EXAMPLE 216

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-(pyridin-3-ylmethyl)acetamide

LCMS 476/478 $[M+H]^+$, RT 1.6 min.

EXAMPLE 217

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-(2-morpholin-4-ylethyl)acetamide

LCMS 498/500 $[M+H]^+$, RT 1.5 min.

EXAMPLE 218

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-(2-piperidin-1-ylethyl)acetamide

LCMS 496/498 $[M+H]^+$, RT 1.5 min.

EXAMPLE 219

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-[3-(1*H*-imidazol-1-yl)propyl]acetamide

LCMS 493/495 $[M+H]^+$, RT 1.4 min.

EXAMPLE 220

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methyl-*N*-[(1-methyl-1*H*-imidazol-2-yl)methyl]acetamide

LCMS 493/495 $[M+H]^+$, RT 1.5 min.

EXAMPLE 221

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 468/470 $[M+H]^+$, RT 1.5 min.

EXAMPLE 222

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-(cyclopropylmethyl)acetamide

LCMS 439/441 $[M+H]^+$, RT 2.1 min.

EXAMPLE 223

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-1,3-thiazol-2-ylacetamide

LCMS 468/470 $[M+H]^+$, RT 2.1 min.

EXAMPLE 224

Formic acid - 2-{4-[(5-chloro-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-*N*-methylacetamide (1:1)

To a solution of Intermediate 25 (1.4 g) and Intermediate 24 (1.9 g) in DMF (30 ml) was added TEA (2.8 ml) This mixture was heated at 100°C for 3.5 hours. More Intermediate 24 (0.5 g) and TEA (0.3 ml) were added and heating continued at 100°C for another 3.5 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on reverse phase silica eluting with 0-100% (MeOH + 0.04% formic acid)/(H_2O + 0.04% formic acid) to give the title compound as a brown foam (1.17 g, 50%). LCMS 400/402 $[M+H]^+$, RT 2.43 min. ^{1}H NMR 300 MHz (d_6-DMSO) 9.75 (1H, s, br), 8.70 (1H, s, br), 8.40 (1H, s), 8.20 (1H, s), 7.75 (1H, d), 7.7-7.6 (2H, m), 7.55 (1H, t), 7.15 (1H, t), 3.8-3.6 (1H, s, br), 2.95 (2H, s), 2.85-2.75 (2H, m), 2.60 (2H, d), 2.25-2.10 (2H, m), 2.00-1.85 (2H, m), 1.70-1.50 (2H, m).

EXAMPLE 225

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylpropanamide

Prepared in similar manner to Example 33 from the bis HCl salt of Example 32 (40 mg) and 2-chloro-*N*-methylpropanamide (CAS 42275-47-8) (16 mg). Purification by prep HPLC (Method B) afforded the title compound as an off-white powder (5.8 mg, 10%). LCMS (pH 5.8) 413/415 $[M+H]^+$, RT 2.81 min. ^{1}H NMR 300 MHz (d_4-MeOD) 8.65 (1H, d), 8.50 (1H, s), 8.15 (1H, s), 7.45 (1H, d), 7.30-7.15 (2H, m), 3.95 (1H, s, br), 3.15 (1H, q), 2.95 (2H, t), 2.80 (3H, s), 2.50 (1H, t), 2.35 (1H, t), 2.15 (2H, m), 1.70 (2H, dq), 1.30 (3H, d).

EXAMPLE 226

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methyl-2-phenylacetamide

Prepared in similar manner to Example 33 from the bis HCl salt of Example 32 (68 mg) and 2-chloro-*N*-methyl-2-phenylacetamide (CAS 7899-96-4) (42 mg). Purification by prep HPLC (Method A) afforded the title compound as a yellow solid (8.9 mg, 10%). LCMS 475/477 [M+H]+, RT 2.18 min. 1H NMR 300 MHz (d_4-MeOH) 8.60 (1H, d), 8.50 (1H, s), 8.15 (1H, s), 7.50-7.40 (3H, m), 7.40-7.30 (3H, m), 7.25 (1H, t), 7.15 (1H, s), 3.95 (1H, s, br), 3.85 (1H, s), 3.05 (1H, d), 2.80-2.70 (1H, hidden by solvent), 2.65 (3H, s), 2.35 (1H, t), 2.85 (1H, d), 2.10-1.95 (2H, m), 1.85-1.60 (2H, m).

EXAMPLES 227 and 228

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methyl-2-phenylacetamide

Separation of the enantiomers of Example 226 was achieved by chiral prep HPLC (Mobile phase: 40% IPA, 60% heptane, flow rate: 10 ml/min, run time: 25 min.) Enantiomer 1 was afforded as a yellow solid (8.2 mg). Chiral HPLC (Mobile phase: 40% IPA, 60% heptane, flow rate: 1 ml/min, run time: 25 min.) RT 6.3 min. Enantiomer 2 was afforded as a yellow solid (6.1 mg). Chiral HPLC, RT 12.4 min.

EXAMPLE 229

{4-[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-ylamino]piperidin-1-yl}-(tetrahydrofuran-3-yl)acetonitrile

To a stirred solution of Example 32 (100 mg) in MeCN / water (0.6 ml / 0.4 ml) at r.t. was added sequentially tetrahydrofuran-3-carboxaldehyde (50 % in H_2O) (0.17 ml), NaCN (92 mg) and AcOH (0.082 ml). After 5 hours the mixture was poured into water (10 ml) and the resulting precipitate removed by filtration, washed with water and dried *in vacuo* to give the title product as a white solid (86 mg, 66 % yield). LCMS 410/412 $[M+H]^+$, RT 3.43 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.65 (1H, s, br), 8.50 (1H, s, br), 8.25 (1H, s), 7.50 (1H, d), 7.30 (1H, dd), 7.21 (1H, t), 7.12 (1H, t), 4.00-3.50 (7H, m), 3.10-2.50 (3H, m), 2.50-1.40 (7H, m).

EXAMPLE 230

tert-Butyl 4-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)(cyano)methyl]piperidine-1-carboxylate

Prepared in similar manner to Example 229 from Example 32 (196 mg) and 4-formyl-piperidine-1-carboxylic acid *tert*-butyl ester (CAS 137076-22-3) (250 mg) to give the title compound as a brown solid (355 mg, quantitative). LCMS 523 $[M\text{-}HCN]^+$, 549 [M-H], RT 4.32 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.88 (1H, s, br), 8.63 (1H, s, br), 8.49 (1H, s, br), 8.25 (1H, s), 7.50 (1H, d), 7.31 (1H, d), 7.23 (1H, t), 7.12 (1H, t), 6.43 (1H, d), 4.41 (1H, dd), 4.05-3.75 (3H, m), 3.70 (1H, d), 2.96-2.57 (4H, m), 2.12-1.89 (2H, m), 1.86-0.94 (8H, m), 1.38 (9H, s).

EXAMPLE 231

2-{4-[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-ylamino]piperidin-1-yl}-3-phenyl-propionitrile

Prepared in similar manner to Example 229 from Example 32 (180 mg) and phenylacetaldehyde (0.185 ml) to give the title compound as a light brown solid (116 mg, 46%). LCMS 430 $[M\text{-}HCN]^+$, 455 [M-H], RT 4.06 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.88 (1H, s, br), 8.65 (1H, s, br), 8.51 (1H, s, br), 8.26 (1H, s), 7.49 (1H, d), 7.40-7.10 (8H, m), 4.14 (1H, dd), 3.90 (1H, m, br), 3.15 (1H, m), 3.04 (2H, m), 2.91 (1H, m), 2.45 (1H, m), 2.23 (1H, m), 2.12-1.93 (2H, m), 1.60 (2H, m).

EXAMPLE 232

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-(tetrahydrofuran-3-yl)acetamide bis(hydrochloride)

To a stirred solution of Example 229 (30 mg) in DMSO/water (1.5 ml) was added a solution of H_2O_2/NaOH (1:1, 15 % in H_2O) (1.5 ml) at room temperature. After 2 hours the reaction was concentrated *in vacuo* and purified by prep HPLC (Method C). The resulting product was treated with HCl (1.0 M in EtOH) and concentrated *in vacuo* to give the title compound as an orange oil (13 mg, 43%). LCMS 455 $[M+H]^+$ (Free base) RT 1.86 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.86 (1H, s, br), 8.58 (1H, s, br), 8.48 (1H, s, br), 8.22 (1H, s), 8.13 (1H, s), 7.48 (1H, d), 7.38 (1H, d), 7.18 (2H, m), 7.10 (2H, m), 3.85-3.55 (4H, m), 3.0-2.79 (3H, m), 2.63 (1H, m), 2.30 (1H, m), 2.02- 1.80 (3H, m), 1.61-1.35 (3H, m).

EXAMPLE 233

2-{4-[5-Chloro-4-(1*H*-indol-3-yl)-pyrimidin-2-ylamino]-piperidin-1-yl}-2-piperidin-4-yl-acetamide

To a stirred solution of Example 230 (200 mg) in DMSO / H_2O (5 ml) at 0°C was added a solution of H_2O_2/NaOH (1:1, 15 % in H_2O) (5 ml) and the resulting solution

warmed to r.t. over 10 min. After 3 hours the reaction was poured into water (20 ml) and the resulting precipitate was collected by filtration. This solid was suspended in HCl (2.0 M in H_2O) (3 ml) and the mixture heated to 160°C in a microwave for 3 min. The reaction mixture was allowed to cool to r.t. and concentrated *in vacuo*. A portion of the resulting residue was purified by prep HPLC (Method C) to give the title compound as an orange glassy solid (13 mg). LCMS 468 $[M+H]^+$, RT 1.53 min. ^1H NMR 300 MHz (d_4-MeOD) 8.64 (1H, m), 8.50 (1H, s), 8.21 (1H, s), 8.10(1H, s), 7.48 (1H, m), 7.22 (2H, m), 4.12 (1H, s, br), 3.60-3.35 (5H, m), 3.15-3.0 (4H, m), 2.47-2.28 (3H, m), 2.17 (1H, m), 2.00-1.80 (3H, m), 1.72-1.55 (2H, m).

EXAMPLE 234

3-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)dihydrofuran-2(3*H*)-one

The bis HCl salt of Example 32 (60 mg), α-bromo-γ-butyrolactone (12.4 µl) and TEA (140 µl) were stirred at r.t. in MeCN (5 ml) for 48 hours. More α-bromo-γ-butyrolactone (15 µl) and DMF (1 ml) were added and the mixture heated in a sealed tube at 100°C for 20 minutes in a microwave. The solvent was removed *in vacuo*. Purification of the residue by prep HPLC (Method A) afforded the title compound as an off-white solid (23.6 mg, 38%). LCMS 412/414 $[M+H]^+$, RT 2.03 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s), 8.65 (1H, s, br), 8.45 (1H, s), 8.25 (1H, s), 7.50 (1H, d), 7.35-7.1 (3H, m), 4.30 (1H, m), 4.15 (1H, q), 3.95-3.65 (2H, m), 3.60-3.20 (1H hidden by water), 3.05 (1H, d), 2.85-2.45 (2H, m), 2.45-2.15 (2H, m), 1.95 (2H, m), 1.55 (2H, m).

EXAMPLE 235

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(5-nitro-1,3-thiazol-2-yl)piperidin-4-yl]pyrimidin-2-amine

To a solution of the bis HCl salt of Example 32 (100 mg) in dry DMF (5 ml) under nitrogen was added 2-bromo-5-nitrothiazole (52 mg) and K_2CO_3 (138 mg). The reaction was stirred at r.t. overnight. Water (30 ml) was added to the reaction mixture and the resulting precipitate was collected by filtration. This was washed with water and dried *in vacuo* to afford the title compound as a yellow solid (100mg, 88%). LCMS 456/458 $[M+H]^+$, RT 3.85 min. ^1H NMR 400 MHz (d_6-DMSO) 8.558 (1H, d), 8.42 (1H, m), 8.35 (1H, s), 8.28 (1H, s), 7.50 (1H, d), 7.10-7.25 (3H, m), 4.10-4.25 (2H, m), 3.50 (2H, m), 2.18 (2H, m), 1.75 (2H, qd), 1.30 (1H, s).

EXAMPLE 236

6-(4-{[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)nicotinonitrile

Prepared in a similar way to Example 235 from the bis HCl salt of Example 32 (100 mg), Na_2CO_3 (190 mg) and 6-chloronicotinonitrile (50 mg). Purification by column chromatography on silica eluting with 0-50% EtOAc/heptane yielded the title compound as an off-white solid (29 mg, 37%). LCMS 430/432 $[M+H]^+$, RT 3.83 min. ^1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.62 (1H, s, br), 8.50 (2H, m), 8.30 (1H, s), 7.85 (1H, dd), 7.50 (1H, d), 7.32 (1H, d), 7.20 (2H, m), 7.0 (1H, d), 4.50 (2H, d), 4.15 (1H, m), 3.15 (2H, t), 2.05 (2H, s, br), 1.50 (2H, q).

EXAMPLE 237

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-pyridin-2-ylpiperidin-4-yl)pyrimidin-2-amine

The bis HCl salt of Example 32 (50 mg) and bromopyridine (12 µl) were suspended in NMP (3 ml) and Na_2CO_3 (53 mg) added. The reaction was heated at 180°C in the microwave reactor for 80 min. The solvent was removed *in vacuo* and the dried material was purified by prep HPLC (Method A) to give the title compound as a dark brown solid (13mg, 25%). LCMS 405/407 $[M+H]^+$, RT 2.16 min. ^1H NMR 300 MHz (d_6-DMSO) 11.90 (1H, s, br), 8.68 (1H, s, br), 8.50 (1H, s), 8.35 (1H, s), 8.10 (1H, m), 7.50 (2H, m), 7.30 (1H, d), 7.20 (2H, m), 6.85 (1H, d), 6.60 (1H, m), 4.35 (2H, d), 4.10 (1H, s, br), 3.00 (2H, t), 2.00 (2H, s, br), 1.50 (2H, m).

EXAMPLE 238

N-[1-(5-Aminopyridin-2-yl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

The bis HCl salt of Example 32 (150 mg) and 2-chloro-5-nitropyridine (59.3 mg) were suspended in DMF (4 ml) and Na_2CO_3 (159 mg) added. The reaction mixture was stirred for 5 hours at r.t. under nitrogen. Water (20 ml) was added and the resulting yellow precipitate was filtered off and dried *in vacuo*. This solid was dissolved in EtOH/water (36 ml/9 ml) and tin (II) chloride (535 mg) added. This mixture was heated at 100°C for 6 hours, basified with saturated $NaHCO_3$ solution, filtered and washed with MeOH. The filtrate was concentrated *in vacuo* and the residue stirred with thiol resin for 20 min. The mixture was filtered and concentrated *in vacuo* to give the title compound as a purple solid (25mg, 22%). LCMS 420/422 $[M+H]^+$, RT 2.07 min. ^1H NMR 300 MHz (d_6-DMSO) 10.0 (1H, s), 8.65 (1H, s, br), 8.50 (1H, m), 8.20 – 8.30 (2H, m), 7.61 (1H, d), 7.50 (1H, d), 7.30 (1H, m), 7.10-7.20 (2H, m), 6.70 (1H, d), 4.60 (1H, s, br), 4.25 (2H, d), 4.05 (2H, d), 2.0 (2H, s, br), 1.55 (2H, s, br).

EXAMPLE 239

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-pyrimidin-2-ylpiperidin-4-yl)pyrimidin-2-amine

Prepared in a similar manner as Example 237 from the bis HCl salt of Example 32 (100 mg) and 2-chloropyrimidine (28.6 mg) to give the title compound as a light brown solid (13 mg, 25%). LCMS 406/408 $[M+H]^+$, RT 3.62 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.65 (1H, s, br), 8.50 (1H, s, br), 8.35 (1H, d), 8.28 (1H, s), 7.50 (1H, d), 7.30 (1H, d), 7.20 (2H, m), 6.60 (1H, t), 4.70 (2H, d), 4.12 (1H, br), 3.05 (2H, t, br), 2.05 (2H, br), 1.48 (2H, m, br).

EXAMPLE 240

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-pyrazin-2-ylpiperidin-4-yl)pyrimidin-2-amine

Prepared in a similar manner to Example 237 from the bis HCl salt of Example 32 (100 mg) and 2-chloropyrazine (30 mg). Purification by prep HPLC (Method A) afforded the title compound as a light brown solid (13mg, 25%). LCMS 406/408 $[M+H]^+$, RT 3.42 min. ^{1}H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.65 (1H, br, s), 8.50 (1H, br), 8.38 (1H, s), 8.29 (1H, s), 8.10 (1H, m), 7.80 (1H, m), 7.50 (1H, d), 7.30 (1H, d), 7.10-7.20 (2H, m), 4.40 (2H, d), 4.10 (1H, s, br), 3.05 (2H, t, br), 2.05 (2H, br), 1.45-1.65 (2H, m).

EXAMPLE 241

2-(4-{[5-Chloro-4-(7-cyano-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

To a solution of Intermediate 31 (145 mg) in DMF (5 ml) was added sodium carbonate (180 mg) and Intermediate 24 (99 mg). The reaction mixture was heated to 100°C for 2 hrs. More Intermediate 24 (99 mg) and TEA (0.05ml) were added and the reaction mixture heated to 100°C overnight. The reaction mixture was concentrated *in vacuo* and purified by prep HPLC (Method C) to afford the title compound as a white solid (15.9 mg, 8%). LCMS 424/426 $[M+H]^+$, RT 1.93 min. ^{1}H NMR 300 MHz (d_4-MeOH) 8.85 (1H, d), 8.50 (1H, s), 8.15 (1H, s), 7.60-7.55 (1H, m), 7.30-7.25 (1H, m), 4.00-3.85 (1H, m), 3.20 (2H, s), 3.10-3.00 (2H, m), 2.80 (3H, s), 2.65-2.55 (2H, m), 2.20-2.10 (2H, m), 1.80-1.65 (2H, m).

EXAMPLE 242

tert-Butyl 4-{[5-chloro-4-(7-cyano-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

To a solution of Intermediate 31 (50 mg) in EtOH (5 ml) was added TEA (16 µl) and 1-BOC-4-amino-piperidine (35 mg). The reaction mixture was heated at reflux for 20 hours. More 1-BOC-4-aminopiperidine (210 mg) and TEA (0.14ml) were added and the reaction heated to reflux for a further 4 days. The reaction was concentrated *in vacuo* and purified by prep HPLC (Method C) to afford the title compound as an off-white solid (17.6 mg, 33%). LCMS 451/453 $[M-H]^+$, RT 4.24 min. ^1H NMR 300 MHz ($CDCl_3$) 9.10 (1H, br, s), 8.30 (1H, d), 8.45 (1H, m), 8.30 (1H, s), 7.60 (1H, d), 7.35-7.25 (1H, m), 5.10 (1H, d), 4.15-4.00 (3H, m), 3.05-2.90 (2H, m), 2.15-2.10 (2H, m), 1.55-1.40 (11H, m).

EXAMPLE 243

4-{[5-Chloro-4-(6-cyano-1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

To a solution of Intermediate 32 (2 g) in dry THF (45 ml) under nitrogen at –78°C was added *n*-BuLi (1.6M in hexanes) (5.81ml) dropwise to maintain the temperature at -78°C. After 15 minutes a solution of zinc bromide (dried *in vacuo* for 2 days) in THF (15 ml) was added maintaining the temperature at -78°C. After 1 hour the reaction mixture was allowed to warm to r.t. and stirred for a further hour. 2,4,5-trichloro-pyrimidine (900 mg), and tetrakis(triphenylphosphine)palladium(0) (142 mg) were added and the reaction mixture heated to 90°C for 18 hours. The reaction mixture was partitioned between water (100 ml) and DCM (100 ml) and the aqueous layer was washed with DCM (3 x 50 ml). The organic fractions were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 0-100% EtOAc/heptane followed by 10%MeOH/EtOAc afforded a solid. A portion of this solid (750 mg) was dissolved in DMF (30 ml) and the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (1.16 g) and Na_2CO_3 (2.01 g) were added to the reaction mixture, which was heated to 80°C for 90 min. After cooling to r.t., the mixture was filtered and solvent removed *in vacuo* to give a crude product. This was suspended in MeOH (5 ml) and KOH (34 mg) added. The reaction mixture was heated at reflux for 90 min. The solvent was removed *in vacuo* and the residue purified by prep HPLC (Method C) to afford the title compound as a yellow solid (14mg). LCMS 424/426, $[M-H]^+$, RT 3.63. ^1H NMR 300 MHz (d_6-DMSO) 8.45 (1H, s), 8.05 (1H, s), 7.90 (1H, d), 7.70 (1H, s), 7.40 (1H, d), 4.30-4.20 (1H, m), 3.95-3.85 (2H, m), 3.10-3.00 (2H, q), 2.90-2.80 (2H, m), 1.90-1.80 (2H, m), 1.45-1.30 (2H, m), 1.05-0.95 (3H, t).

EXAMPLE 244

tert-Butyl 4-[(4-imidazo[1,2-a]pyridin-3-yl-5-methylpyrimidin-2-yl)amino]piperidine-1-carboxylate

To a suspension/solution of 4-amino-1-tert-butoxycarbonyl piperidine (1.0 g) in dry MeCN (10 ml) under nitrogen was added TEA (1.7 ml) followed by 3,5-dimethyl-pyrazole-1-carboxamidine nitrate (1.1 g). The reaction mixture was heated at 60°C overnight. The reaction mixture was allowed to cool to r.t. and the solvent removed *in vacuo* to afford a light beige sticky gum (1.2 g). A portion of this compound (0.3 g) was dissolved in dry DMF (10 ml) under nitrogen and Intermediate 33 (0.15 g) was added followed by NaOMe (0.13 g). The reaction mixture was heated at 100°C for 3 days. The mixture was allowed to cool to r.t. and the DMF was removed *in vacuo*. The residue was partitioned between water (50 ml) and EtOAc (150 ml). The organic layer was washed with water (50 ml), washed with brine (50ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 0-2% MeOH/EtOAc gave a light brown semi-solid. Trituration in Et_2O afforded the title compound as a flesh coloured solid (35 mg, 13%). LCMS 409 $[M+H]^+$, RT 2.30 min. ^1H NMR 300 MHz ($CDCl_3$) 9.69 (1H, d), 8.23 (1H, s), 8.15 (1H, s), 7.75 (1H, d), 7.36 (1H, t), 6.94 (1H, t), 4.95 (1H, d), 4.20-3.95 (3H, m), 3.05-2.90 (2H, m), 2.40 (3H, s), 2.15-2.05 (2H, m), 1.55-1.40 (2H, m), 1.50 (9H, s).

EXAMPLE 245

N-ethyl-4-[(4-imidazo[1,2-a]pyridin-3-yl-5-methylpyrimidin-2-yl)amino]piperidine-1-carboxamide

To a solution of Example 244 (25 mg) in MeOH / DCM (3 ml / 3 ml) was added a solution of HCl (1.0M in Et_2O) (1.2 ml) and the reaction mixture was stirred at r.t. for 18 hours. The solvent was removed *in vacuo* to give a lemon yellow solid. This was dissolved/suspended in dry DCM (15 ml) under nitrogen and to this added TEA (40 µl) followed by ethyl isocyanate (5 µl). The reaction mixture was stirred at r.t. for 18 hours. DCM (100 ml) was added and the organic layer was washed with water (20 ml), separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as an off-white solid (10.9 mg, 47%). LCMS (pH 5.8) 380 $[M+H]^+$, RT 2.47 min. ^1H NMR 300 MHz (d_4-MeOD) 9.40 (1H, d), 8.23 (1H, s), 8.20 (1H, s), 7.72 (1H, d), 7.53 (1H, t), 7.10 (1H, t), 6.53 (1H partially

exchanging with MeOH, t, br), 4.10-3.94 (3H, m), 3.20 (2H, q), 3.05-2.92 (2H, m), 2.40 (3H, s), 2.12-2.00 (2H, m), 1.60-1.42 (2H, m), 1.12 (3H, t).

EXAMPLE 246

4-{[5-Chloro-4-(1*H*-pyrrolo[3,2-c]pyridin-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

To a solution of Intermediate 35 (70 mg) in dry DMF (5 ml) under nitrogen was added the hydrochloride salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (70 mg) and Na_2CO_3 (89 mg). The mixture was heated at 90°C for 4 hours. The mixture was concentrated *in vacuo* and the residue dissolved in MeOH (20 ml). To this was added KOH (1 pellet) and the mixture stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue was extracted with EtOAc (150 ml). The organic layer was washed with water (40 ml), washed with brine (40 ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by column chromatography on reverse phase silica eluting with 0-100% (MeOH+0.04% formic acid)/(H_2O + 0.04% formic acid) afforded the title compound as a brown solid (7 mg, 10%). LCMS (pH5.8) 400/402 $[M+H]^+$, RT 2.38 min. ^1H NMR 300 MHz (d_6-DMSO) 12.20 (1H, s, br), 10.00-9.60 (1H, d, br), 8.55 (1H, s), 8.35-8.25 (2H, m), 7.60-7.30 (2H, m), 6.50 (1H, t), 4.05-3.80 (3H, m), 3.05 (2H, quin), 2.80 (2H, t), 1.90 (2H, s, br), 1.40 (2H, dq), 1.00 (3H, t).

EXAMPLE 247

4-[(5-Chloro-4-imidazo[1,2-a]pyrimidin-3-ylpyrimidin-2-yl)amino]-*N*-ethylpiperidine-1-carboxamide

Zinc bromide (972 mg) was dried at 130°C under vacuum for 2 hours and then allowed to cool to room temperature. A solution of 3-bromoimidazo[1,2-a]pyrimidine (CAS 6840-45-5) (566 mg) in THF (20 ml) was charged into a three neck round bottomed flask under nitrogen and cooled to –78°C. *n*-BuLi (2.5M in hexanes) (1.4 ml) was added dropwise to the cooled solution, which was left to stir for 30 min. A solution of the dried zinc bromide in THF (10ml) was added dropwise to the cooled mixture and stirred at –78°C. After 30 minutes the reaction mixture was allowed to warm to r.t. over 1 hour. 2,4,5-trichloropyrimidine (534 mg) and tetrakis(triphenylphosphine)palladium(0) (120 mg) were added to the mixture, which was heated to 70°C overnight. The solvent was removed *in vacuo*. Purification by flash chromatography on silica eluting with 10% MeOH/DCM yielded a brown glass (184 mg). A portion of this compound (156 mg) was dissolved in dry DMF (5 ml) and to it added the HCl salt of 4-aminopiperidine-1-

carboxylic acid ethylamide (CAS 675112-80-8) (122 mg) and TEA (0.28 ml). The mixture was heated to 100°C for 4 hours, cooled to room temperature and the solvent removed *in vacuo*. Purification by prep HPLC (Method B) afforded the title compound as an off-white solid (3.8 mg). LCMS (pH 5.8) 401/403 $[M+H]^+$, RT 2.23 min. ^{1}H NMR 300 MHz (d_6-DMSO) 10.40-9.90 (1H, m, br), 8.85 (1H, m), 8.75 (1H, m), 8.45 (1H, s), 7.70 (1H, d), 7.30 (1H, m), 6.50 (1H, t), 4.00-3.80 (3H, m), 3.05 (2H, m), 2.80 (2H, m), 1.90 (2H, m), 1.35 (2H, m), 1.00 (3H, t).

EXAMPLE 248

5-Chloro-4-(1*H*-indol-3-yl)-*N*-piperidin-3-ylpyrimidin-2-amine bis(hydrochloride)

To a solution of Intermediate 2 (1 g) in dry DMF (10 ml) under nitrogen was added (+/-)-3-amino-1-*N*-Boc-piperidine (CAS 184637-48-7) (500 mg) and Na_2CO_3 (1.32 g). The mixture was heated at 110°C for 24 hours, a further 250 mg of (+/-)-3-amino-1-*N*-Boc-piperidine was added and heating continued for another 24 hours. The mixture was cooled to r.t., concentrated *in vacuo* and the residue dissolved in MeOH (20 ml). To this was added KOH (330 mg) and the mixture stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue was extracted with EtOAc (200 ml). The organic layer was washed with water (50 ml), washed with brine (50 ml), separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 10-50% EtOAc/heptane afforded a solid, which was dissolved in DCM (75ml) and treated with 2N HCl in ether (5 ml) for 24 hours. The solvent was removed *in vacuo* and the resulting solid triturated in Et_2O to afford the title compound as a yellow solid (585 mg, 58%). LCMS 328/330 $[M+H]^+$, RT 1.92 min. ^{1}H NMR 300 MHz (d_6-DMSO) 12.00 (1H, s, br), 9.15-8.85 (2H, d, br), 8.80-8.40 (2H, m), 8.35 (1H, s), 7.50 (2H, d), 7.20 (2H, quin), 4.50-4.00 (1H, obscured by water), 3.40 (1H, d), 3.20 (1H, d), 3.00-2.80 (2H, m), 2.10 (1H, m), 1.90 (1H, m), 1.75 (1H, m), 1.60 (1H, m).

EXAMPLE 249

3-{[5-Chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]amino}-N-ethylpiperidine-1-carboxamide

To a suspension of Example 248 (100 mg) in DCM (10 ml) was added DIPEA (130 µl) and ethyl isocyanate (21 µl). The mixture was stirred for 1 hour and the solvent removed *in vacuo*. Purification by column chromatography on silica eluting with 0-10% MeOH/DCM afforded the title compound as a yellow solid (87.3 mg, 89%). LCMS 399/401 $[M+H]^+$, RT 2.97 min. 1H NMR 300 MHz (d_6-DMSO) 11.85 (1H, s, br), 8.90-8.35 (2H, m), 8.25 (1H, s), 7.50 (1H, d), 7.30-7.00 (3H, m), 6.45 (1H, t), 4.05 (1H, d),

3.85 (2H, d), 3.00 (2H, m), 2.70 (2H, t), 2.05 (1H, s, br), 1.70 (1H, dd), 1.45 (2H, m), 0.95 (3H, t).

EXAMPLE 250

4-{[5-Chloro-4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

Indole (357 mg), NaH (60% dispersion in mineral oil) (112mg) and DMF (3 ml) were combined and stirred under nitrogen for 15 min at r.t.. To this suspension was then added dropwise a cold solution of 2,4,5-trichloropyrimidine (567 mg) in DMF (2ml). The reaction mixture was stirred at r.t. for 2 hours before being quenched by the addition of water (5 ml) and extracted with EtOAc (3 x 100 ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was partially purified by column chromatography on silica eluting with 5% EtOAc/heptane to afford a yellow solid (605 mg). A portion of this solid (150 mg), the HCl salt of 4-aminopiperidine-1-carboxylic acid ethylamide (CAS 675112-80-8) (142 mg), sodium carbonate (200 mg) and DMF (3.5 ml) were combined and heated to 95°C for 4 hours. The reaction was left to cool overnight and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (50 ml) and washed with water (15 ml). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was partially purified by prep HPLC (method C) and then triturated in Et_2O to afford the title compound as a white powder (147 mg, 48%). LCMS 399/401 $[M+H]^+$, RT 3.62 min. ^1H NMR 300 MHz (d_4-MeOH) 8.41 (1H, s), 7.92-7.85 (1H, d), 7.82-7.75 (1H, d), 7.7-7.67 (1H, d), 7.3-7.12 (2H, m), 6.7 (1H, d), 4.1-3.92 (3H, m), 3.25-3.12 (2H, m), 3.0-2.85 (2H, t), 2.1-1.98 (2H, m), 1.6-1.4 (2H, m), 1.15-1.05 (3H, t).

EXAMPLE 251

2-(4-{[5-Chloro-4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

Prepared in a similar manner to Example 250 from 2-(4-aminopiperidin-1-yl)-*N*-methylacetamide bis(hydrochloride) (167 mg). Purification by prep HPLC (Method C) followed by trituration in Et_2O afforded the title compound as a white powder (134 mg, 44%). LCMS 399/401 $[M+H]^+$, RT 2.20 min. ^1H NMR 300 MHz (d_4-MeOH) 8.4 (1H, s), 7.92-7.82 (1H, d), 7.80-7.72 (1H, d), 7.70-7.58 (1H, d), 7.38-7.14 (2H, m), 6.7 (1H, d), 5.5 (1H, s), 3.9-3.78 (1H, m), 3.1 (1H, s), 2.95-2.85 (1H, d), 2.8 (3H, s), 2.42-2.28 (2H, t), 2.1-1.98 (2H, d), 1.82-1.64 (2H, m).

EXAMPLE 252

Formic acid - *N*-ethyl-4-{[4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxamide (1:1)

Example 250 (50 mg), NaOH (6 mg) and palladium on carbon (10% Pd) (catalytic amount) were combined in MeOH (6 ml) and stirred under hydrogen for 3 hours. The reaction mixture was then neutralised with an aqueous 1M HCl solution and the catalyst was filtered off through a pad of celite, washing with EtOH. The solvents were removed *in vacuo* and the crude material was purified by prep HPLC (Method C) to afford the title compound as a white solid (15 mg, 33%). LCMS 365 $[M+H]^+$ (Free base), RT 2.39 min. ^1H NMR 300 MHz (d_4-MeOH) 8.72-8.60 (1H, d), 8.25-8.2 (1H, d), 7.91-7.85 (1H, d), 7.65-7.55 (1H, d), 7.35-7.25 (1H, t), 7.25-7.15 (1H, t), 6.9-6.82 (1H, d), 6.8-6.72 (1H, d), 4.18-4.0 (3H, d), 3.28-3.15 (2H, q), 3.1-2.95 (2H, t), 2.2-2.05 (2H, d), 1.63-1.45 (2H, m), 1.2-1.05 (3H, t).

EXAMPLE 253

Formic acid - 2-(4-{[4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide (1:1)

Prepared in a similar manner to Example 252 from Example 251 (50 mg). Purification by prep HPLC (Method C) afforded the title compound as a white solid (27 mg, 60%). LCMS 365 $[M+H]^+$ (Free base), RT 1.70 min. ^1H NMR 300 MHz (d_4-MeOH) 8.7-8.58 (1H, d), 8.3-8.18 (1H, d), 7.92-7.85 (1H, d), 7.65-7.55 (1H, d), 7.35-7.25 (1H, t), 7.25-7.15 (1H, d), 6.92-6.85 (1H, d), 6.75-6.70 (1H, d), 4.12-3.85 (1H, m), 3.5 (2H, s), 3.3-3.18 (2H, m), 2.9-2.75 (3H, t), 2.32-2.18 (2H, d), 2.0-1.8 (2H, m).

EXAMPLE 254

Formic acid - [4-(4-imidazo[1,2-*a*]pyridin-3-yl-pyrimidin-2-ylamino)-piperidin-1-yl]-(4-methyl-piperazin-1-yl)-methanone (1:1)

To a solution of Example 121 (70 mg) in DCM (5ml) under nitrogen was added 4-methyl-1-piperazine carbonyl chloride (35 mg) and TEA (0.14 ml) and the reaction stirred at r.t. for 18 hours. The solvent was removed *in vacuo* and the residue purified by column chromatography on reverse phase silica eluting with 0-100% (MeOH + 0.04% formic acid)/(H_2O + 0.04% formic acid) to give the title compound as a yellow solid (52.4 mg, 72%). LCMS (pH 5.8) 421 $[M+H]^+$ (Free base) RT 2.06 min. ^1H NMR 300 MHz (d_4-MeOH) 10.20-10.10 (1H, m) 8.40 (1H, s), 8.28 (1H, s), 8.25 (1H, d), 8.20 (1H, s), 7.70 (1H, d), 7.55 (1H, tr), 7.15 (1H, tr), 7.12 (1H, d), 4.15-4.00 (1H, m), 3.85-3.75 (2H, m),

3.50-3.40 (4H, m), 3.20-3.05 (2H, m), 3.05-2.92 (4H, m), 2.70 (3H, s), 2.20-2.10 (2H, m), 1.70-1.50 (2H, m).

The following examples were prepared using methods similar to those described above.

EXAMPLE 255

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(1-methylpiperidin-4-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 453/455 $[M+H]^+$, RT 1.93 min.

EXAMPLE 256

4-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-3-methyl-4-oxobutanamide

LCMS 441/443 $[M+H]^+$, RT 2.55 min.

EXAMPLE 257

4-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*,3-dimethyl-4-oxobutanamide

LCMS 455/457 $[M+H]^+$, RT 2.63 min.

EXAMPLE 258

4-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*,*N*,3-trimethyl-4-oxobutanamide

LCMS 469/471 $[M+H]^+$, RT 2.83 min.

EXAMPLE 259

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(3-methylbutanoyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 412/414 $[M+H]^+$, RT 3.53 min.

EXAMPLE 260

N-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]-*N*-methyltetrahydro-2*H*-pyran-4-carboxamide

LCMS 397/399 $[M+H]^+$, RT 4.32 min.

EXAMPLE 261

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(1-methyl-1*H*-imidazol-4-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 436/438 $[M+H]^+$, RT 2.28 min.

EXAMPLE 262

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-3-phenylpropanamide

LCMS 475/477 $[M+H]^+$, RT 2.08 min.

EXAMPLE 263

N-[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]-*N,N,N*-trimethylurea

LCMS 470/472 $[M+H]^+$, RT 2.72 min.

EXAMPLE 264

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(1-methylpiperidin-4-yl)piperidine-1-carboxamide

LCMS 468/470 $[M+H]^+$, RT 1.96 min.

EXAMPLE 265

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-isopropylpiperidine-1-carboxamide

LCMS 413/415 $[M+H]^+$, RT 3.95 min.

EXAMPLE 266

N-[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-1-(hydroxymethyl)-2-oxoethyl]acetamide (Racemate)

LCMS 457/459 $[M+H]^+$, RT 2.34 min.

EXAMPLE 267

N-[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-1-(hydroxymethyl)-2-oxoethyl]acetamide (Enantiomer 1)

LCMS 457/459 $[M+H]^+$, RT 2.36 min.

EXAMPLE 268

N-[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-1-(hydroxymethyl)-2-oxoethyl]acetamide (Enantiomer 2)

LCMS 457/459 $[M+H]^+$, RT 2.35 min.

EXAMPLE 269

5-Chloro-*N*-{1-[(1,1-dioxidotetrahydro-3-thienyl)acetyl]piperidin-4-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine (Racemate)

LCMS 488/490 $[M+H]^+$, RT 2.83 min.

EXAMPLE 270

5-Chloro-*N*-{1-[(1,1-dioxidotetrahydro-3-thienyl)acetyl]piperidin-4-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine (Enantiomer 1)

LCMS 488/490 $[M+H]^+$, RT 2.83 min.

EXAMPLE 271

5-Chloro-*N*-{1-[(1,1-dioxidotetrahydro-3-thienyl)acetyl]piperidin-4-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine (Enantiomer 2)

LCMS 488/490 $[M+H]^+$, RT 2.83 min.

EXAMPLE 272

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(1-methylpiperidin-3-yl)piperidine-1-carboxamide

LCMS 468/470 $[M+H]^+$, RT 1.94 min.

EXAMPLE 273

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-cyclopropylpiperidine-1-carboxamide

LCMS 411/413 $[M+H]^+$, RT 2.85 min.

EXAMPLE 274

N-[1-(1-Acetylprolyl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 467/469 $[M+H]^+$, RT 2.64 min.

EXAMPLE 275

N-[1-(2-azetidin-1-yl-2-oxoethyl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 425/427 $[M+H]^+$, RT 1.98 min.

EXAMPLE 276

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(tetrahydrofuran-3-ylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 455/457 $[M+H]^+$, RT 2.57 min.

EXAMPLE 277

1-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-3-ol

LCMS 441/443 $[M+H]^+$, RT 2.57 min.

EXAMPLE 278

3-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}dihydrofuran-2(3*H*)-one

LCMS 469/471 $[M+H]^+$, RT 2.04 min.

EXAMPLE 279

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(tetrahydro-2*H*-pyran-4-ylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 469/471 $[M+H]^+$, RT 1.95 min.

EXAMPLE 280

tert-Butyl 3-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]azetidine-1-carboxylate

LCMS 512/513 $[M+H]^+$, RT 3.54 min.

EXAMPLE 281

N-[1-(Azetidin-3-ylcarbonyl)piperidin-4-yl]-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 411/413 $[M+H]^+$, RT 1.86 min.

EXAMPLE 282

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide (S-Enantiomer)

LCMS 399/401$[M+H]^+$, RT 2.96 min.

EXAMPLE 283

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide (R-Enantiomer)

LCMS 399/401$[M+H]^+$, RT 2.96 min.

EXAMPLE 284

1-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-3-ol

LCMS 441/443 $[M+H]^+$, RT 2.56 min.

EXAMPLE 285

tert-Butyl 3-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidine-1-carboxylate

LCMS (pH 5,8) 525/527 $[M+H]^+$, RT 3.86 min.

EXAMPLE 286

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(isopropylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS (pH 5.8) 427/429 $[M+H]^+$, RT 2.60 min.

EXAMPLE 287

tert-Butyl 3-{[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}azetidine-1-carboxylate

LCMS 540/542 $[M+H]^+$, RT 2.29 min.

EXAMPLE 288

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(tetrahydro-2*H*-pyran-4-yl)piperidine-1-carboxamide

LCMS 455/457 $[M+H]^+$, RT 2.74 min.

EXAMPLE 289

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(pyrrolidin-3-ylcarbonyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 427/429 $[M+H]^+$, RT 1.94 min.

EXAMPLE 290

1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]prolinamide

LCMS 482 $[M+H]^+$, RT 1.9 min.

EXAMPLE 291

2-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}butanoic acid

LCMS 471 $[M+H]^+$, RT 2.2 min.

EXAMPLE 292

2-[[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl](propyl)amino]ethanol

LCMS 471 $[M+H]^+$, RT 2.1 min.

EXAMPLE 293

N-(2-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}ethyl)acetamide

LCMS 470 $[M+H]^+$, RT 1.9 min.

EXAMPLE 294

2-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}-1-phenylethanol

LCMS 505 $[M+H]^+$, RT 2.2 min.

EXAMPLE 295

2-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}cyclohexanol

LCMS 483 $[M+H]^+$, RT 2.1 min.

EXAMPLE 296

4-[[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl](ethyl)amino]butan-1-ol

LCMS 485 $[M+H]^+$, RT 2.0 min.

EXAMPLE 297

2-[[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl](2-methylbutyl)amino]ethanol

LCMS 499 $[M+H]^+$, RT 2.3 min.

EXAMPLE 298

4-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperazin-2-one

LCMS 468 $[M+H]^+$, RT 2.0 min.

EXAMPLE 299

Methyl *N*-[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]serinate

LCMS 487 $[M+H]^+$, RT 2.0 min.

EXAMPLE 300

4-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}butan-2-ol

LCMS 457 $[M+H]^+$, RT 2.0 min.

EXAMPLE 301

2-{*tert*-Butyl[2-(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}ethanol

LCMS 485 $[M+H]^+$, RT 1.9 min.

EXAMPLE 302

2-[[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl](methyl)amino]acetamide

LCMS 456 $[M+H]^+$, RT 1.9 min.

EXAMPLE 303

6-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}hexan-1-ol

LCMS 485 $[M+H]^+$, RT 2.0 min.

EXAMPLE 304

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-({[(5-methyl-4*H*-1,2,4-triazol-3-yl)methyl]amino}acetyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 480 $[M+H]^+$, RT 1.9 min.

EXAMPLE 305

5-Chloro-*N*-(1-{[[(3,5-dimethyl-1*H*-pyrazol-4-yl)methyl](methyl)amino]acetyl}piperidin-4-yl)-4-(1H-indol-3-yl)pyrimidin-2-amine

LCMS 507 $[M+H]^+$, RT 2.0 min.

EXAMPLE 306

2-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}-4-methylpentan-1-ol

LCMS 485 $[M+H]^+$, RT 2.2 min.

EXAMPLE 307

{1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]pyrrolidin-2-yl}methanol

LCMS 469 $[M+H]^+$, RT 2.0 min.

EXAMPLE 308

1-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}propan-2-ol

LCMS 443/445 $[M+H]^+$, RT 1.92 min.

EXAMPLE 309

2-{[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]amino}-3-methylpentan-1-ol

LCMS 485 $[M+H]^+$, RT 2.2 min.

EXAMPLE 310

1-[2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidin-3-ol

LCMS 469 $[M+H]^+$, RT 2.0 min.

EXAMPLE 311

N-{1-[(1-Acetylpyrrolidin-3-yl)carbonyl]piperidin-4-yl}-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 467/469 $[M+H]^+$, RT 2.61 min.

EXAMPLE 312

1-Acetyl-5-[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-3-ol

LCMS 493/495 $[M+H]^+$, RT 2.28 min and 2.39 min (Rotamers).

EXAMPLE 313

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-{[methyl(tetrahydro-2*H*-pyran-4-yl)amino]acetyl}piperidin-4-yl)pyrimidin-2-amine

LCMS (pH 5.8) 483/485 $[M+H]^+$, RT 2.69 min.

EXAMPLE 314

N-{1-[(Azetidin-3-ylamino)acetyl]piperidin-4-yl}-5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 440/442 $[M+H]^+$, RT 1.69 min.

EXAMPLE 315

1-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]azetidin-3-ol

LCMS 427/429 $[M+H]^+$, RT 2.53 min.

EXAMPLE 316

2-{3-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]azetidin-1-yl}-*N*-methylacetamide

LCMS (pH 5.8) 482/484 $[M+H]^+$, RT 2.69 min.

EXAMPLE 317

2-(3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide (Racemate)

LCMS 399/401 $[M+H]^+$, RT 1.92 min.

EXAMPLE 318

2-(3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide (R Enantiomer)

LCMS (pH 5.8) 399/401 $[M+H]^+$, RT 3.26 min.

EXAMPLE 319

2-(3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide (S Enantiomer)

LCMS 399/401 $[M+H]^+$, RT 1.88 min.

EXAMPLE 320

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-isopropylpiperidine-1-carboxamide (Enantiomer 1)

LCMS 413/415 $[M+H]^+$, RT 3.20 min.

EXAMPLE 321

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-isopropylpiperidine-1-carboxamide (Enantiomer 2)

LCMS 413/415 $[M+H]^+$, RT 3.19 min.

EXAMPLE 322

2-{3-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-1-yl}-*N*-methylacetamide (Racemate)

LCMS (pH 5.8) 496/498 $[M+H]^+$, RT 2.79 min.

EXAMPLE 323

2-{3-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-1-yl}-*N*-methylacetamide (Enantiomer 1)

LCMS 496/498 $[M+H]^+$, RT 1.91 min.

EXAMPLE 324

2-{3-[(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]pyrrolidin-1-yl}-*N*-methylacetamide (Enantiomer 2)

LCMS 496/498 $[M+H]^+$, RT 1.95 min.

EXAMPLE 325

N-Azetidin-3-yl-4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidine-1-carboxamide

LCMS 425/427 $[M+H]^+$, RT 1.89 min.

EXAMPLE 326

tert-Butyl 3-{[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]amino}piperidine-1-carboxylate

LCMS 554/556 $[M+H]^+$, RT 3.59 min.

EXAMPLE 327

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-piperidin-3-ylpiperidine-1-carboxamide

LCMS 454/456 $[M+H]^+$, RT 1.95 min.

EXAMPLE 328

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(1-methylpiperidin-3-yl)piperidine-1-carboxamide

LCMS 468/470 $[M+H]^+$, RT 1.98 min.

EXAMPLE 329

tert-Butyl 3-{[(4-{[5-chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)carbonyl]amino}piperidine-1-carboxylate

LCMS 554/556 $[M+H]^+$, RT 3.59 min.

EXAMPLE 330

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(1-methylpiperidin-3-yl)piperidine-1-carboxamide

LCMS 468/470 $[M+H]^+$, RT 1.99 min.

EXAMPLE 331

4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-piperidin-3-ylpiperidine-1-carboxamide

LCMS 454/456 $[M+H]^+$, RT 1.93 min.

EXAMPLE 332

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-piperidin-4-ylacetamide (Enantiomer 1)

LCMS 468/470 $[M+H]^+$, RT 1.49 min.

EXAMPLE 333

2-(4-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-piperidin-4-ylacetamide (Enantiomer 2)

LCMS 468/470 $[M+H]^+$, RT 1.49 min.

EXAMPLE 334

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(1*H*-tetrazol-5-ylacetyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 438/440 $[M+H]^+$, RT 2.57 min.

EXAMPLE 335

5-Chloro-4-(1*H*-indol-3-yl)-*N*-[1-(1-oxidopyridin-2-yl)piperidin-4-yl]pyrimidin-2-amine

LCMS (pH 5.8) 421/423 $[M+H]^+$, RT 2.76 min.

EXAMPLE 336

5-Chloro-*N*-{1-[(5,5-dimethylmorpholin-2-yl)acetyl]piperidin-4-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 483/485 $[M+H]^+$, RT 2.05 min.

EXAMPLE 337

5-Chloro-*N*-[1-(1*H*-imidazol-5-ylacetyl)piperidin-4-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine

LCMS (pH 5.8) 436/438 $[M+H]^+$, RT 2.69 min.

EXAMPLE 338

5-Chloro-4-(1*H*-indol-3-yl)-*N*-(1-pyridin-2-ylpiperidin-3-yl)pyrimidin-2-amine (S Enantiomer)

LCMS 405/407 $[M+H]^+$, RT 2.28 min.

EXAMPLE 339

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(1-methylpiperidin-4-yl)carbonyl]piperidin-3-yl}pyrimidin-2-amine (R Enantiomer)

LCMS 453/455 $[M+H]^+$, RT 2.00 min.

EXAMPLE 340

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(4-methylpiperazin-1-yl)carbonyl]piperidin-3-yl}pyrimidin-2-amine (R Enantiomer)

LCMS (pH 5.8) 454/456 $[M+H]^+$, RT 2.79 min.

EXAMPLE 341

5-Chloro-*N*-{1-[(dimethylamino)acetyl]piperidin-3-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine (R Enantiomer)

LCMS (pH 5.8) 413/415 $[M+H]^+$, RT 2.61 min.

EXAMPLE 342

5-Chloro-*N*-{1-[(dimethylamino)acetyl]piperidin-3-yl}-4-(1*H*-indol-3-yl)pyrimidin-2-amine (S Enantiomer)

LCMS 413/415 $[M+H]^+$, RT 1.96 min.

EXAMPLE 343

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(methylamino)acetyl]piperidin-3-yl}pyrimidin-2-amine (R Enantiomer)

LCMS (pH 5.8) 399/401 $[M+H]^+$, RT 2.51 min.

EXAMPLE 344

5-Chloro-4-(1*H*-indol-3-yl)-*N*-{1-[(methylamino)acetyl]piperidin-3-yl}pyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 399/401 $[M+H]^+$, RT 2.48 min.

EXAMPLE 345

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-piperidin-4-ylpiperidine-1-carboxamide (R Enantiomer)

LCMS 454/456 $[M+H]^+$, RT 1.91 min.

EXAMPLE 346

1-[2-(3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]piperidin-4-ol (R Enantiomer)

LCMS (pH 5.8) 469/471 $[M+H]^+$, RT 2.55 min.

EXAMPLE 347

3-{[5-Chloro-4-(1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-(1-methylpiperidin-4-yl)piperidine-1-carboxamide (R Enantiomer)

LCMS (pH 5.8) 468/470 $[M+H]^+$, RT 2.54 min.

EXAMPLE 348

5-Chloro-*N*-[1-(1*H*-imidazol-2-ylmethyl)piperidin-3-yl]-4-(1*H*-indol-3-yl)pyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 408/410 $[M+H]^+$, RT 2.86 min.

EXAMPLE 349

5-Chloro-4-(1-methyl-1*H*-indol-3-yl)-*N*-piperidin-4-ylpyrimidin-2-amine

LCMS 342/344 $[M+H]^+$, RT 2.06 min.

EXAMPLE 350

2-(4-{[5-Chloro-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS 413/415 $[M+H]^+$, RT 2.05 min.

EXAMPLE 351

4-{[5-Chloro-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

LCMS 413/415 $[M+H]^+$, RT 3.25 min.

EXAMPLE 352

5-Chloro-*N*-{1-[(dimethylamino)acetyl]piperidin-4-yl}-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-amine

LCMS 427/429 $[M+H]^+$, RT 2.18 min.

EXAMPLE 353

4-{[5-Chloro-4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-piperidin-4-ylpiperidine-1-carboxamide

LCMS 468/470 $[M+H]^+$, RT 2.16 min.

EXAMPLE 354

4-{[5-Chloro-4-(7-cyano-1*H*-indol-3-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

LCMS 424/426 $[M+H]^+$, RT 3.06 min.

EXAMPLE 355

3-(5-Chloro-2-{[1-(5-oxoprolyl)piperidin-4-yl]amino}pyrimidin-4-yl)-1*H*-indole-7-carbonitrile

LCMS 464/466 $[M+H]^+$, RT 2.68 min.

EXAMPLE 356

N-[2-(4-{[5-Chloro-4-(7-cyano-1*H*-indol-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-2-oxoethyl]acetamide

LCMS 452/454 $[M+H]^+$, RT 2.69 min.

EXAMPLE 357

5-Chloro-4-(1H-indol-1-yl)-*N*-{1-[(methylamino)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS 399/401 $[M+H]^+$, RT 2.31 min.

EXAMPLE 358

5-Chloro-*N*-{1-[(dimethylamino)acetyl]piperidin-4-yl}-4-(1*H*-indol-1-yl)pyrimidin-2-amine

LCMS 413/415 $[M+H]^+$, RT 2.33 min.

EXAMPLE 359

tert-Butyl 4-{[4-(4-cyano-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

LCMS 363 $[M-t\text{Bu}]^+$, RT 4.01 min.

EXAMPLE 360

2-(4-{[5-Chloro-4-(4-cyano-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS 424/426 $[M+H]^+$, RT 2.17 min.

EXAMPLE 361

2-(4-{[4-(4-Cyano-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS (pH 2) 390 $[M+H]^+$, RT 1.86 min.

EXAMPLE 362

1-(2-{[1-(*N*,*N*-Dimethylglycyl)piperidin-4-yl]amino}pyrimidin-4-yl)-1*H*-indole-4-carbonitrile

LCMS 404 $[M+H]^+$, RT 1.90 min.

EXAMPLE 363

2-(4-{[5-Chloro-4-(1*H*-pyrrolo[3,2-b]pyridin-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS 400/402 $[M+H]^+$, RT 1.16 min.

EXAMPLE 364

tert-Butyl 4-{[4-(1*H*-pyrrolo[3,2-b]pyridin-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

LCMS 339 $[M-t\text{Bu}]^+$, 2.35 min.

EXAMPLE 365

tert-Butyl 4-{[5-chloro-4-(1*H*-pyrrolo[3,2-b]pyridin-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

LCMS 373 $[M-t\text{Bu}]^+$, RT 2.72 min.

EXAMPLE 366

N-Methyl-2-(4-{[4-(1*H*-pyrrolo[3,2-b]pyridin-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)acetamide

LCMS 366 $[M+H]^+$, RT 1.04 min.

EXAMPLE 367

tert-Butyl 4-{[4-(4-amino-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

LCMS 353 $[M-t\text{Bu}]^+$, RT 2.53 min.

EXAMPLE 368

tert-Butyl 4-{[4-(4-amino-1*H*-indol-1-yl)-5-chloropyrimidin-2-yl]amino}piperidine-1-carboxylate

LCMS 343/345 $[M-t\text{Bu}]^+$, RT 3.66 min.

EXAMPLE 369

4-{[4-(4-Amino-1*H*-indol-1-yl)-5-chloropyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

LCMS 414/416 $[M+H]^+$, RT 2.39 min.

EXAMPLE 370

4-{[4-(4-Amino-1*H*-indol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

LCMS (pH 5.8) 380 $[M+H]^+$, RT 2.61 min.

EXAMPLE 371

2-(4-{[4-(4-Amino-1*H*-indol-1-yl)-5-chloropyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS 363 $[M-t\text{Bu}]^+$, RT 4.01 min.

EXAMPLE 372

2-(4-{[4-(4-Amino-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS (pH 5.8) 380 $[M+H]^+$, RT 2.28 min.

EXAMPLE 373

tert-Butyl 4-{[4-(4-methoxy-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate

LCMS 368 $[M-t\text{Bu}]^+$, RT 3.66 min.

EXAMPLE 374

4-{[5-Chloro-4-(4-methoxy-1*H*-indol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide

LCMS (pH 5.8) 429/431 $[M+H]^+$, RT 3.68 min.

EXAMPLE 375

2-(4-{[5-Chloro-4-(4-methoxy-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS (pH 5.8) 429/431 $[M+H]^+$, RT 3.42 min.

EXAMPLE 376

N-Ethyl-4-{[4-(4-methoxy-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxamide

LCMS (pH 5.8) 395 $[M+H]^+$, RT 3.34 min.

EXAMPLE 377

2-(4-{[4-(4-Methoxy-1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS 395 $[M+H]^+$, RT 2.31 min.

EXAMPLE 378

tert-Butyl 4-({5-chloro-4-[4-(dimethylamino)-1*H*-indol-1-yl]pyrimidin-2-yl}amino)piperidine-1-carboxylate

LCMS 471/473 $[M+H]^+$, RT 3.53 min.

EXAMPLE 379

tert-Butyl 4-({4-[4-(dimethylamino)-1*H*-indol-1-yl]pyrimidin-2-yl}amino)piperidine-1-carboxylate

LCMS 437 $[M+H]^+$, RT 2.81 min.

EXAMPLE 380

4-({4-[4-(Dimethylamino)-1*H*-indol-1-yl]pyrimidin-2-yl}amino)-*N*-ethylpiperidine-1-carboxamide

LCMS (pH 5.8) 408 $[M+H]^+$, RT 3.29 min.

EXAMPLE 381

2-[4-({4-[4-(Dimethylamino)-1*H*-indol-1-yl]pyrimidin-2-yl}amino)piperidin-1-yl]-*N*-methylacetamide

LCMS (pH 5.8) 408 $[M+H]^+$, RT 3.06 min.

EXAMPLE 382

tert-Butyl 4-({4-[4-(aminocarbonyl)-1*H*-indol-1-yl]pyrimidin-2-yl}amino)piperidine-1-carboxylate

LCMS 337 $[M-t\text{Bu}]^+$, RT 3.53 min.

EXAMPLE 383

1-[2-({1-[2-(Methylamino)-2-oxoethyl]piperidin-4-yl}amino)pyrimidin-4-yl]-1*H*-indole-4-carboxamide

LCMS (pH 5.8) 408 $[M+H]^+$, RT 2.07 min.

EXAMPLE 384

N-Methyl-2-(4-{[4-(1*H*-pyrrolo[2,3-b]pyridin-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)acetamide

LCMS 366 $[M+H]^+$, RT 1.58 min.

EXAMPLE 385

tert-Butyl 3-{[5-chloro-4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidine-1-carboxylate (S Enantiomer)

LCMS 372/374 $[M-t\text{Bu}]^+$, RT 4.72 min.

EXAMPLE 386

3-{[5-Chloro-4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide (S Enantiomer)

LCMS 399/401 $[M+H]^+$, RT 3.70 min.

EXAMPLE 387

3-{[5-Chloro-4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}-*N*-ethylpiperidine-1-carboxamide (R Enantiomer)

LCMS (pH 5.8) 399/401 $[M+H]^+$, RT 3.79 min.

EXAMPLE 388

2-(3-{[5-Chloro-4-(1*H*-indol-1-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide (R Enantiomer)

LCMS (pH 5.8) 399/401 $[M+H]^+$, RT 3.94 min.

EXAMPLE 389

N-[1-(3-Furoyl)piperidin-4-yl]-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-amine

LCMS 389 $[M+H]^+$, RT 1.83 min.

EXAMPLE 390

2-{4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-*N*-methyl-2-phenylacetamide

LCMS (pH 5.8) 442 $[M+H]^+$, RT 2.91 min.

EXAMPLE 391

6-{4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}nicotinonitrile

LCMS 397 $[M+H]^+$, RT 4.32 min.

EXAMPLE 392

4-Imidazo[1,2-a]pyridin-3-yl-*N*-{1-[(4-methylpiperazin-1-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS (pH 5.8) 420 $[M+H]^+$, RT 2.06 min.

EXAMPLE 393

4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]-*N*-methoxypiperidine-1-carboxamide

LCMS 368 $[M+H]^+$, RT 1.42 min.

EXAMPLE 394

4-({4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}carbonyl)-1,3-oxazolidin-2-one

LCMS 408 $[M+H]^+$, RT 2.20 min.

EXAMPLE 395

4-Imidazo[1,2-a]pyridin-3-yl-*N*-[1-(morpholin-4-ylacetyl)piperidin-4-yl]pyrimidin-2-amine

LCMS (pH 5.8) 422 $[M+H]^+$, RT 2.32 min.

EXAMPLE 396

4-Imidazo[1,2-a]pyridin-3-yl-*N*-{1-[(1-methyl-1*H*-imidazol-4-yl)carbonyl]piperidin-4-yl}pyrimidin-2-amine

LCMS (pH 5.8) 403 $[M+H]^+$, RT 2.25 min.

EXAMPLE 397

4-Imidazo[1,2-a]pyridin-3-yl-*N*-{1-[(3-methylisoxazol-5-yl)acetyl]piperidin-4-yl}pyrimidin-2-amine

LCMS (pH 5.8) 418 $[M+H]^+$, RT 2.58 min.

EXAMPLE 398

4-Imidazo[1,2-a]pyridin-3-yl-*N*-[1-(3-methylbutanoyl)piperidin-4-yl]pyrimidin-2-amine

LCMS 379 $[M+H]^+$, RT 1.97 min.

EXAMPLE 399

2-{4-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-2-piperidin-4-ylacetamide

LCMS 435 $[M+H]^+$, RT 1.94 min.

EXAMPLE 400

N-{1-[(Dimethylamino)acetyl]piperidin-4-yl}-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-amine

LCMS (pH 5.8) 380 $[M+H]^+$, RT 1.91 min.

EXAMPLE 401

4-(6-Bromoimidazo[1,2-a]pyridin-3-yl)-*N*-piperidin-4-ylpyrimidin-2-amine

LCMS (pH 5.8) 373/375 $[M+H]^+$, RT 1.90 min.

EXAMPLE 402

2-(4-{[4-(6-Bromoimidazo[1,2-a]pyridin-3-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS 444/446 $[M+H]^+$, RT 2.46 min.

EXAMPLE 403

2-(4-{[4-(8-Bromoimidazo[1,2-a]pyridin-2-yl)pyrimidin-2-yl]amino}piperidin-1-yl)-*N*-methylacetamide

LCMS 444/446 $[M+H]^+$, RT 1.42 min.

EXAMPLE 404

N-Ethyl-4-[(4-imidazo[1,2-a]pyridin-3-yl-5-methoxypyrimidin-2-yl)amino]piperidine-1-carboxamide

LCMS (pH 5.8) 396 $[M+H]^+$, RT 2.46 min.

EXAMPLE 405

2-{4-[(4-Imidazo[1,2-a]pyridin-3-yl-5-methoxypyrimidin-2-yl)amino]piperidin-1-yl}-*N*-methylacetamide

LCMS (pH 5.8) 396 $[M+H]^+$, RT 2.23 min.

EXAMPLE 406

N-Ethyl-3-[(4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidine-1-carboxamide (S Enantiomer)

LCMS (pH 5.8) 366 $[M+H]^+$, RT 2.45 min.

EXAMPLE 407

N-Ethyl-3-[(4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidine-1-carboxamide (R Enantiomer)

LCMS (pH 5.8) 366 $[M+H]^+$, RT 2.43 min.

EXAMPLE 408

2-{3-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-*N*-methylacetamide (S Enantiomer)

LCMS (pH 5.8) 366 $[M+H]^+$, RT 2.43 min.

EXAMPLE 409

2-{3-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-*N*-methylacetamide (R Enantiomer)

LCMS (pH 5.8) 366 $[M+H]^+$, RT 2.38 min.

EXAMPLE 410

N-(2-{3-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidin-1-yl}-2-oxoethyl)acetamide (S Enantiomer)

LCMS (pH 5.8) 394 $[M+H]^+$, RT 2.12 min.

EXAMPLE 411

4-Imidazo[1,2-a]pyridin-3-yl-*N*-{1-[(1-methylpiperidin-4-yl)carbonyl]piperidin-3-yl}pyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 418 $[M-H]^-$, RT 1.99 min.

EXAMPLE 412

N-{1-[(Dimethylamino)acetyl]piperidin-3-yl}-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 380 $[M+H]^+$, RT 1.95 min.

EXAMPLE 413

4-Imidazo[1,2-a]pyridin-3-yl-*N*-{1-[(methylamino)acetyl]piperidin-3-yl}pyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 366 $[M+H]^+$, RT 1.98 min.

EXAMPLE 414

3-[(4-Imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]-*N*-3-thienylpiperidine-1-carboxamide (S Enantiomer)

LCMS (pH 5.8) 420 $[M+H]^+$, RT 2.88 min.

EXAMPLE 415

N-[1-(1*H*-imidazol-5-ylacetyl)piperidin-3-yl]-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 403 $[M+H]^+$, RT 2.08 min.

EXAMPLE 416

4-Imidazo[1,2-a]pyridin-3-yl-*N*-{1-[(4-methylpiperazin-1-yl)carbonyl]piperidin-3-yl}pyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 421 $[M+H]^+$, RT 2.11 min.

EXAMPLE 417

N-[1-(1*H*-Imidazol-2-ylmethyl)piperidin-3-yl]-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-amine (R Enantiomer)

LCMS (pH 5.8) 375 $[M+H]^+$, RT 2.14 min.

EXAMPLE 418

N-[1-(1*H*-Imidazol-2-ylmethyl)piperidin-3-yl]-4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-amine (S Enantiomer)

LCMS (pH 5.8) 375 $[M+H]^+$, RT 2.12 min.

EXAMPLE 419

Ethyl 3-[(4-imidazo[1,2-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidine-1-carboxylate (S Enantiomer)

LCMS (pH 5.8) 367 $[M+H]^+$, RT 2.97 min.

EXAMPLE 420

3-[(4-Imidazo[1,2-a]pyridin-2-ylpyrimidin-2-yl)amino]-*N,N*-dimethylpiperidine-1-carboxamide (S Enantiomer)

LCMS 366 $[M+H]^+$, RT 1.71 min.

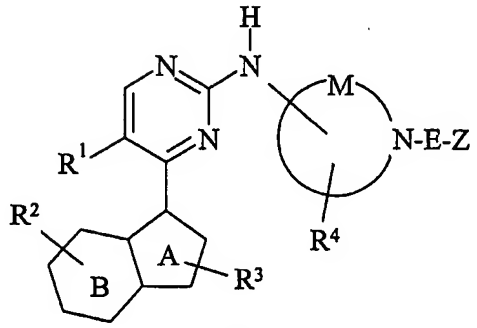
EXAMPLE 421

N-Ethyl-4-[(4-pyrazolo[1,5-a]pyridin-3-ylpyrimidin-2-yl)amino]piperidine-1-carboxamide

LCMS 366 $[M+H]^+$, RT 1.73 min.

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof:



(I)

wherein

A represents a pyrrole, pyrazole, imidazole or triazole ring;

B represents a benzene, pyridine or pyrimidine ring;

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

E represents a covalent bond or an optionally substituted straight or branched alkylene chain containing from 1 to 4 carbon atoms; wherein the optional substituents are selected from cyano, aminocarbonyl, C_{1-6}alkylaminocarbonyl and di(C_{1-6})alkylaminocarbonyl;

Z represents hydrogen, $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-COCO_2R^b$, $-COCONR^cR^d$, $-COCH_2NR^cR^d$, $-COCH_2NR^cCONR^cR^d$, $-COCH_2NR^cCO_2R^b$, $-NR^cCOR^a$, $-NR^cCO_2R^b$, $-NR^cCONR^cR^d$, $-SO_2R^e$, $-SO_2NR^cR^d$ or $-SO_2NR^cCO_2R^b$; or Z represents an optionally substituted phenyl, heteroaryl or C_{3-7} heterocycloalkyl group;

R^1 and R^2 independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylsulphonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, aminocarbonyl or C_{2-6} alkoxycarbonyl;

R^3 represents hydrogen, C_{1-6} alkyl, $-CH_2CONR^cR^d$ or $-SO_2R^e$;

R^4 represents hydrogen, C_{1-6} alkoxy, oxo, $-CO_2R^b$ or $-CONR^cR^d$;

R^a represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents;

R^b represents hydrogen or C_{1-6} alkyl;

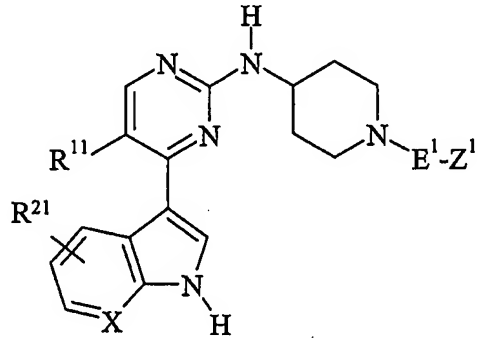
R^c is as defined above for R^a, and R^d represents hydrogen, C_{1-6} alkyl or hydroxy(C_{1-6})alkyl; or R^c and R^d, when taken together with the nitrogen atom to which they are both attached, represent azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl, any of which groups may be optionally substituted by C_{1-6} alkyl or hydroxy; and

R^e is as defined above for R^a.

2. A compound according to Claim 1 wherein A represents a pyrrole, imidazole or triazole ring.

3. A compound according to Claim 1 or 2 wherein R^4 represents hydrogen.

4. A compound according to Claim 1 represented by formula (II) or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof:



(II)

wherein

R^{11} represents hydrogen, halogen, cyano or C_{1-6} alkyl;

R^{21} represents hydrogen, halogen or cyano;

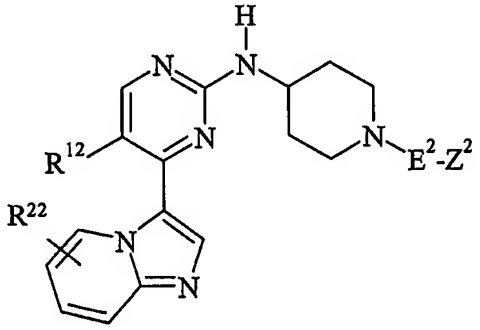
E^1 represents a covalent bond or a methylene linkage;

Z^1 represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, $-CONR^cOR^b$, $-SO_2NHCO_2R^b$ or $-COCH_2NR^cR^d$;

and

R^a, R^b, R^c, R^d and X are as defined in Claim 1.

5. A compound according to Claim 1 represented by formula (IIA) or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof:



(IIA)

wherein

R^{12} represents hydrogen, halogen or C_{1-6} alkyl;

R^{22} represents hydrogen or halogen;

E^2 represents a covalent bond or a methylene linkage;

Z^2 represents $-COR^a$, $-CO_2R^b$, $-CONR^cR^d$, SO_2R^e or $-COCH_2NR^cR^d$; and

R^a, R^b, R^c, R^d and R^e are as defined in Claim 1.

6. A pharmaceutical composition comprising a compound of formula (I) as defined in Claim 1, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, in association with one or more pharmaceutically acceptable carriers.

7. The use of a compound of formula (I) as defined in Claim 1, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, for the manufacture of a medicament for the treatment and/or prevention of autoimmune and inflammatory disorders; vascular disorders; neurodegenerative disorders; metabolic disorders; oncological conditions; pain and nociceptive disorders; and ophthalmic disorders.

8. A method for the treatment and/or prevention of autoimmune and inflammatory disorders; vascular disorders; neurodegenerative disorders; metabolic disorders; oncological conditions; pain and nociceptive disorders; and ophthalmic disorders which comprises administering to a patient in need of such treatment an effective amount of a compound of of formula (I) as defined in Claim 1, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/003827

A. CLASSIFICATION OF SUBJECT MATTER
C07D401/14 C07D403/14 C07D405/14 C07D409/14 C07D413/14
C07D417/14 C07D471/04 A61K31/506 A61P25/28 A61P27/02
A61P29/00 A61P31/00 A61P35/00 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/00207 A (MERCK & CO., INC; GOULET, JOUNG, L; HOLMES, MARK, A; HUNT, JULIANNE, A) 4 January 2001 (2001-01-04) page 83 - page 135; examples 6-70	1-3,6-8
P,X	WO 2004/089913 A (NOVARTIS AG; NOVARTIS PHARMA GMHBH; BOLLBUCK, BIRGIT; DENHOLM, ALASTAI) 21 October 2004 (2004-10-21) cited in the application page 155 - page 197; examples 204-272	1-8
A	WO 03/106455 A (APPLIED RESEARCH SYSTEMS ARS HOLDING N.V; GAILLARD, PASCALE; GOTTELAND) 24 December 2003 (2003-12-24) page 116; example 91 page 133; example 122 page 135; example 125	1,6-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 2005	28/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Duval, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/003827

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/053942 A1 (ALBERTI MICHAEL JOHN ET AL) 18 March 2004 (2004-03-18) pages 63-66; examples 102-114 page 1, paragraph 8 -----	1,6-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/003827

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/003827

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0100207 A	04-01-2001	AU 6605200 A	31-01-2001
		CA 2376957 A1	04-01-2001
		EP 1206260 A1	22-05-2002
		JP 2003503351 T	28-01-2003
WO 2004089913 A	21-10-2004	NONE	
WO 03106455 A	24-12-2003	AU 2003251721 A1	31-12-2003
		CA 2487948 A1	24-12-2003
US 2004053942 A1	18-03-2004	AU 8231801 A	04-03-2002
		BR 0113448 A	17-06-2003
		CA 2420024 A1	28-02-2002
		EP 1311507 A1	21-05-2003
		WO 0216359 A1	28-02-2002
		HU 0400757 A2	28-07-2004
		JP 2004506736 T	04-03-2004
		MX PA03001593 A	04-06-2003
		NO 20030779 A	07-04-2003
		PL 362130 A1	18-10-2004